



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US97/05558 <b>(22) International Filing Date:</b> 4 April 1997 (04.04.97) <b>(30) Priority Data:</b> 08/629,608 9 April 1996 (09.04.96) US 60/032,263 3 December 1996 (03.12.96) US <b>(71) Applicants:</b> NPS PHARMACEUTICALS, INC. [US/US]; Suite 240, 420 Chipeta Way, Salt Lake City, UT 84108-1256 (US). SMITHKLINE BEECHAM PLC [GB/GB]; Three New Horizons Court, Great West Road, Brentford, Middlesex TW8 9EP (GB). SMITHKLINE BEECHAM [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). <b>(72) Inventors:</b> VAN WAGENEN, Bradford, C.; 3969 South 3250 East, Salt Lake City, UT 84124 (US). DEL MAR, Eric, G.; 2967 E. St. Mary's Circle, Salt Lake City, UT 84108 (US). SHEEHAN, Derek; 6696 South Royal Harvest Way #30, Salt Lake City, UT 84121 (US). BARMORE, Robert, M.; 1172 East Sunnyside Avenue, Salt Lake City, UT 84108 (US). KEENAN, Richard, M.; 796 Bass Cove, Malvern, PA 19355 (US). KOTTECHA, Nikesh, R.; Sai Krupa, 22 Martlesham Welwyn, Garden City, Hertfordshire AL7 2KO (GB). THOMPSON, Mervyn; Cold Harbour Road, The	<b>(74) Agents:</b> HEBER, Sheldon, O. et al.; Lyon & Lyon L.L.P., Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US). <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> CALCILYTIC COMPOUNDS  <b>(57) Abstract</b>  The present invention features calcilytic compounds. "Calcilytic compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of calcilytic compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional calcilytic compounds.		

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DESCRIPTION

## CALCILYTIC COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to compounds able to inhibit calcium receptor activity and the use of such compounds. Preferably, the compounds described herein are administered to patients to achieve a therapeutic effect.

BACKGROUND OF THE INVENTION

5 Certain cells in the body respond not only to chemical signals, but also to ions such as extracellular calcium ions ( $\text{Ca}^{2+}$ ). Extracellular  $\text{Ca}^{2+}$  is under tight homeostatic control and regulates various processes such as blood clotting, nerve and muscle excitability, and proper bone formation.

10 Calcium receptor proteins enable certain specialized cells to respond to changes in extracellular  $\text{Ca}^{2+}$  concentration. For example, extracellular  $\text{Ca}^{2+}$  inhibits the secretion of parathyroid hormone (PTH) from parathyroid cells, inhibits bone resorption by osteoclasts, and  
15 stimulates secretion of calcitonin from C-cells.

PTH is the principal endocrine factor regulating  $\text{Ca}^{2+}$  homeostasis in the blood and extracellular fluids. PTH, by acting on bone and kidney cells, increases the level of  $\text{Ca}^{2+}$  in the blood. This increase in extracellular  $\text{Ca}^{2+}$  then acts  
20 as a negative feedback signal, depressing PTH secretion. The reciprocal relationship between extracellular  $\text{Ca}^{2+}$  and PTH secretion forms an important mechanism maintaining bodily  $\text{Ca}^{2+}$  homeostasis.

Extracellular  $\text{Ca}^{2+}$  acts directly on parathyroid cells to  
25 regulate PTH secretion. The existence of a parathyroid cell surface protein which detects changes in extracellular  $\text{Ca}^{2+}$

has been confirmed. (Brown et al., *Nature* 366:574, 1993.)  
In parathyroid cells, this protein, the calcium receptor,  
acts as a receptor for extracellular  $\text{Ca}^{2+}$ , detects changes in  
the ion concentration of extracellular  $\text{Ca}^{2+}$ , and initiates a  
5 functional cellular response, PTH secretion.

Extracellular  $\text{Ca}^{2+}$  can exert effects on different cell  
functions, reviewed in Nemeth et al., *Cell Calcium* 11:319,  
1990. The role of extracellular  $\text{Ca}^{2+}$  in parafollicular (C-  
cells) and parathyroid cells is discussed in Nemeth, *Cell*  
10 *Calcium* 11:323, 1990. These cells were shown to express  
similar calcium receptors. (See, Brown et al., *Nature*  
366:574, 1993; Mithal et al., *J. Bone Miner. Res.* 9, Suppl.  
1, s282, 1994; Rogers et al., *J. Bone Miner. Res.* 9, Suppl.  
1, s409, 1994; Garrett et al., *Endocrinology* 136:5202-5211,  
15 1995.) The role of extracellular  $\text{Ca}^{2+}$  on bone osteoclasts is  
discussed by Zaidi, *Bioscience Reports* 10:493, 1990.

The ability of various molecules to mimic extracellular  
 $\text{Ca}^{2+}$  in vitro is discussed in references such as Nemeth et  
al., in "Calcium-Binding Proteins in Health and Disease,"  
20 1987, Academic Press, Inc., pp. 33-35; Brown et al.,  
*Endocrinology* 128:3047, 1991; Chen et al., *J. Bone Miner.*  
*Res.* 5:581, 1990; and Zaidi et al., *Biochem. Biophys. Res.*  
*Commun.* 167:807, 1990.

Nemeth et al., PCT/US92/07175, International Publication  
25 Number WO 93/04373, Nemeth et al., PCT/US93/01642,  
International Publication Number WO 94/18959, and Nemeth et  
al., PCT/US94/12117, International Publication Number WO  
95/11211, feature calcium receptor-active molecules and refer  
to calcilytics as compounds able to inhibit calcium receptor  
30 activity. For example, WO 94/18959 on page 8, lines 2-13  
asserts:

Applicant is also the first to describe methods by  
which molecules active at these  $\text{Ca}^{2+}$  receptors can

be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or calcilytics which are active at  $\text{Ca}^{2+}$  receptors. Such calcimimetics or calcilytics are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides such as hormones, enzymes or growth factors, the expression and/or secretion of which is regulated or affected by activity at one or more  $\text{Ca}^{2+}$  receptors.

The references provided in the background are not admitted to be prior art to the pending claims.

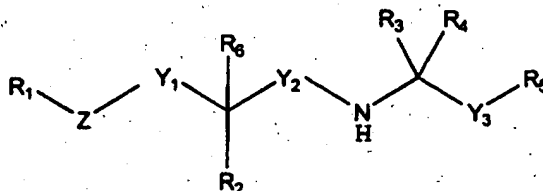
#### SUMMARY OF THE INVENTION

The present invention features calcilytic compounds. "Calcilytic compounds" refer to compounds able to inhibit calcium receptor activity. The ability of a compound to "inhibit calcium receptor activity" means that the compound causes a decrease in one or more calcium receptor activities evoked by extracellular  $\text{Ca}^{2+}$ .

The use of calcilytic compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient are described below. Also described below are techniques which can be used to obtain additional calcilytic compounds.

An example of featured calcilytic compounds are Structure I  $\alpha, \alpha$ -disubstituted arylalkylamine derivatives having the chemical formula:

STRUCTURE I



where  $R_1$  is selected from the group consisting of: aryl, longer-length alk, and cycloalk;

$R_2$  is selected from the group consisting of: lower alk, cycloalk, alkoxy, H, OH, =O, C(O)OH, C(O)O-lower alk, C(O)NH-lower alk, C(O)N(lower alk)<sub>2</sub>, SH, S-lower alk, NH<sub>2</sub>, NH-lower alk, and N(lower alk)<sub>2</sub>;

$R_3$  and  $R_4$  is each independently lower alk or together cyclopropyl;

$R_5$  is aryl;

$R_6$  if present is either hydrogen, lower alkyl or lower alkenyl, wherein  $R_6$  is not present if  $R_7$  is =O;

$Y_1$  is either covalent bond, alkylene, or alkenylene;

$Y_2$  is alkylene;

$Y_3$  is alkylene; and

$Z$  is selected from the group consisting of: covalent bond, O, S, NH, N-lower alk, alkylene, alkenylene, and alkynylene, provided that if  $Z$  is either O, S, NH, or N-lower alk, then  $Y_1$  is not a covalent bond, further provided that  $Y_1$  and  $Z$  may together be a covalent bond;

and pharmaceutically acceptable salts and complexes thereof.

The terms aryl, longer-length alk, lower alk, cycloalk, alkoxy, alkylene, alkenylene, and alkynylene, along with possible substituents are defined in Section II, *infra*.

Section II, *infra*, also provides definitions for other chemical groups described in the present application.

Preferred calcilytic compounds have an  $IC_{50} \leq 50 \mu M$ , more preferably an  $IC_{50} < 10 \mu M$ , and even more preferably an  $IC_{50} < 1 \mu M$ , as measured using the "Calcium Receptor Inhibitor Assay" described in Example 1, *infra*.

Thus, a first aspect of the present invention features a method of treating a patient by administering to

the patient a therapeutically effective amount of a Structure I  $\alpha, \alpha$ -disubstituted arylalkylamine derivative. Treatment can be carried out, for example, to retard the disease in a patient having a disease or to prophylactically retard or prevent the onset of a disease.

A therapeutically effective amount is the amount of compound which achieves a therapeutic effect by retarding a disease in a patient having a disease or prophylactically retarding or preventing the onset of a disease. Preferably, it is an amount which relieves to some extent one or more symptoms of a disease or disorder in a patient; returns to normal either partially or completely one or more physiological or biochemical parameters associated with or causative of the disease or disorder; and/or reduces the likelihood of the onset of the disease or disorder.

A "patient" refers to a mammal in which compounds characterized by their ability to inhibit calcium receptor activity, *in vivo* or *in vitro*, will have a beneficial effect. Preferably, the patient is a human being.

Patients benefiting from the administration of a therapeutic amount of a calcilytic compound can be identified using standard techniques known to those in the medical profession. Diseases or disorders which can be treated by inhibiting one or more calcium receptor activities include one or more of the following types: (1) those characterized by an abnormal bone and mineral homeostasis; (2) those characterized by an abnormal amount of an extracellular or intracellular messenger whose production can be affected by one or more calcium receptor activities; (3) those characterized by an abnormal effect (e.g., a different effect in kind or magnitude) of an intracellular or extracellular messenger which can itself be ameliorated by one or more calcium receptor activities; and (4) other diseases or

disorders where inhibition of one or more calcium receptor activities exerts a beneficial effect, for example, in diseases or disorders where the production of an intracellular or extracellular messenger stimulated by receptor activity compensates for an abnormal amount of a different messenger. Examples of extracellular messengers whose secretion and/or effect can be affected by inhibiting calcium receptor activity are believed to include inorganic ions, hormones, neurotransmitters, growth factors, and chemokines. Examples of intracellular messengers include CAMP, cGMP, IP<sub>3</sub>, calcium, magnesium, and diacylglycerol.

Preferably, a patient is a human having a disease or disorder characterized by one or more of the following: (1) an abnormal bone or mineral homeostasis; (2) an abnormal amount of an extracellular or intracellular messenger which is ameliorated by a compound able to effect one or more calcium receptor activities; and (3) an abnormal effect of an intracellular or extracellular messenger which is ameliorated by a compound able to effect one or more calcium receptor activities.

Preferably, the disease or disorder is characterized by an abnormal bone and mineral homeostasis, more preferably calcium homeostasis. Abnormal calcium homeostasis is characterized by one or more of the following activities: (1) an abnormal increase or decrease in serum calcium; (2) an abnormal increase or decrease in urinary excretion of calcium; (3) an abnormal increase or decrease in bone calcium levels, for example, as assessed by bone mineral density measurements; (4) an abnormal absorption of dietary calcium; (5) an abnormal increase or decrease in the production and/or release of messengers which affect serum calcium levels such as PTH and calcitonin; and (6) an abnormal change in the response elicited by messengers which affect serum calcium



levels. The abnormal increase or decrease in these different aspects of calcium homeostasis is relative to that occurring in the general population and is generally associated with a disease or disorder.

5        Preferably, the calcilytic compounds are used to treat diseases or disorders selected from the group consisting of: hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and  
10        osteoporosis.

      Another aspect of the present invention describes a method of treating a patient comprising the step of administering to the patient an amount of a calcilytic compound sufficient to increase serum PTH level. Preferably,  
15        the method is carried out by administering an amount of the compound effective to cause an increase in duration and/or quantity of serum PTH level sufficient to have a therapeutic effect.

      Increasing serum PTH may be used to achieve a  
20        therapeutic effect by retarding a disease in a patient having the disease or prophylactically retarding or preventing the onset of a disease. Prophylactic treatment can be performed, for example, on a person with an abnormally low serum PTH, or on a person without a low serum PTH, but were increasing PTH  
25        has a beneficial effect. An abnormally low serum PTH is a serum PTH level lower than that occurring in the general population, and is preferably an amount associated with a disease or the onset of a disease.

      Increasing serum PTH levels can be used to treat  
30        different types of diseases including bone and mineral related diseases.

      In different embodiments, the compound is administered to a patient to cause an increase in serum PTH having a

duration up to one hour, about one to about twenty-four hours, about one to about twelve hours, about one to about six hours, about one to about five hours, about one to about four hours, about two to about five hours, about two to about four hours, or about three to about six hours.

In additional different embodiments, the compound is administered to a patient to cause an increase in serum PTH up to 0.5 fold, 0.5 to 5 fold, 5 fold to 10 ten fold, and at least 10 fold, greater than peak serum PTH in the patient.

10 The peak serum level is measured with respect to the patient not undergoing treatment.

Another aspect of the present invention features Structure I calcilytic compounds.

Another aspect of the present invention features a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a calcilytic compound described herein. The pharmaceutical composition contains the calcilytic compound in a form suitable for administration into a mammal, preferably, a human being. Preferably, the pharmaceutical composition contains an amount of a calcilytic compound in a proper pharmaceutical dosage form sufficient to exert a therapeutic effect on a human being. However, multiple doses of pharmaceutical compositions may be used to treat a patient.

25 Considerations and factors concerning dosage forms suitable for administration are known in the art and include potential toxic effects, solubility, route of administration, and maintaining activity. For example, pharmaceutical compositions injected into the bloodstream should be soluble.

30 Another aspect of the present invention features a method of screening for Structure I  $\alpha, \alpha$ -disubstituted arylalkylamine derivatives able to inhibit calcium receptor activity. The method involves the steps of contacting a cell

having a calcium receptor with a Structure I  $\alpha,\alpha$ -disubstituted arylalkylamine derivative and measuring the ability of the compound to inhibit calcium receptor activity.

The screening method can be carried out *in vivo* or *in vitro* and is particularly useful to identify those Structure I  $\alpha,\alpha$ -disubstituted arylalkylamine derivatives most able to act as calcilytic compounds. *In vivo* assays include measuring a physiological parameter related to calcium receptor activity, such as serum hormone levels or serum calcium ion concentration. *In vitro* assays include measuring the ability of the calcilytic compound to affect intracellular calcium concentration, or cellular hormone secretion. Examples of hormones levels which can be affected by calcilytic compounds include PTH and calcitonin.

The calcilytic compounds described herein can be used as part of *in vivo* or *in vitro* methods. Preferably, the compounds are used *in vivo* to achieve a beneficial effect in a patient. Examples of *in vitro* uses, and other *in vivo* uses, include use in a method to identify other calcilytic compounds and use as a tool to investigate calcium receptor activity or the physiological effects of inhibiting calcium receptor activity in different organisms.

Other features and advantages of the invention will be apparent from the following detailed description of the invention, examples, and the claims.

#### DETAILED DESCRIPTION OF THE INVENTION

The present application demonstrates the ability of calcilytic compounds to exert a physiologically relevant effect on a cell by illustrating the ability of such compounds to increase PTH secretion and also identifies a target site for calcilytic compounds. The present

application is believed to be the first to demonstrate that calcilytic compounds can increase PTH secretion.

Calcium receptors are present on different cell types and can regulate different responses in different cell types.

5 While the calcilytic compounds described herein are believed to act at a calcium receptor through a calcium receptor-activity modulating site, unless otherwise explicitly stated in the claims that a compound exerts an effect by acting at a calcium receptor through such a site, there is no intention  
10 to limit the claimed methods or compound to requiring inhibition of calcium receptor activity or any particular mode of action. Rather, the present application demonstrates that compounds able to inhibit calcium receptor activity, whose calcilytic activity can be measured in vivo or in  
15 vitro, exert significant physiological effects. For example, the present application demonstrates the ability of different calcilytic compounds to prevent  $\text{Ca}^{2+}$  inhibition of PTH and, thereby, result in an increase in PTH release.

Compounds binding at the calcium receptor-activity  
20 modulating site can be identified using a labeled compound binding to the site in a competition-binding assay format.

Preferred calcilytic compounds described herein are Structure I  $\alpha, \alpha$ -disubstituted arylalkylamine derivatives able to inhibit calcium receptor activity. Other aspects of the  
25 present invention include assays which can be used to identify those Structure I  $\alpha, \alpha$ -disubstituted arylalkylamine derivatives expected to be effective in inhibiting calcium receptor activity, and/or exerting a therapeutic effect in a patient; preferred groups of Structure I  $\alpha, \alpha$ -disubstituted  
30 arylalkylamine derivatives; and the use of the compounds described herein to treat different diseases or disorders.

### I. Calcium Receptor Activity

Calcium receptors respond to changes in extracellular calcium levels. The exact changes resulting from calcium receptor activity depend on the particular receptor and the cell containing the receptor. For example, the *in vitro* effect of calcium on the calcium receptor in a parathyroid cell includes the following:

1. An increase in internal calcium  $[Ca^{2+}]_i$ . The increase is due to the influx of external calcium and/or to the mobilization of internal calcium. Characteristics of the increase in internal calcium include the following:
  - (a) A rapid (time to peak < 5 seconds) and transient increase in  $[Ca^{2+}]_i$  that is refractory to inhibition by  $1 \mu M$   $La^{3+}$  or  $1 \mu M$   $Gd^{3+}$  and is abolished by pretreatment with ionomycin (in the absence of extracellular  $Ca^{2+}$ );
  - (b) The increase is not inhibited by dihydropyridines;
  - (c) The transient increase is abolished by pretreatment for 10 minutes with 10 mM sodium fluoride;
  - (d) The transient increase is diminished by pretreatment with an activator of protein kinase C (PKC), such as phorbol myristate acetate (PMA), mezerein or (-)-indolactam V. The overall effect of the protein kinase C activator is to shift the concentration-response curve of calcium to the right without affecting the maximal response; and
  - (e) Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) does not affect the increase.
2. A rapid (< 30 seconds) increase in the formation of inositol-1,4,5-triphosphate and/or diacylglycerol. Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) does not affect this increase;

3. The inhibition of dopamine- and isoproterenol-stimulated cyclic AMP formation. This effect is blocked by pretreatment with pertussis toxin (100 ng/ml for > 4 hours); and

- 5           4. The inhibition of PTH secretion. Pretreatment with pertussis toxin (100 ng/ml for > 4 hours) does not affect the inhibition of PTH secretion.

Calcilytic activity of a compound can be determined using techniques such as those described in the examples below and those described in publications such as Nemeth et al., PCT/US92/07175, International Publication Number WO 93/04373, Nemeth et al., PCT/US93/01642, International Publication Number WO 94/18959, and Nemeth et al., PCT/US94/12117, International Publication Number WO 95/11211 (each of which are hereby incorporated by reference herein).

Calcilytic activity varies depending upon the cell type in which the activity is measured. For example, calcilytic compounds possess one or more, and preferably all, of the following characteristics when tested on parathyroid cells in vitro:

1. The compound blocks, either partially or completely, the ability of increased concentrations of extracellular  $\text{Ca}^{2+}$  to:

- 25           (a) increase  $[\text{Ca}^{2+}]_i$ ,  
            (b) mobilize intracellular  $\text{Ca}^{2+}$ ,  
            (c) increase the formation of inositol-1,4,5-triphosphate,  
            (d) decrease dopamine- or isoproterenol-stimulated cyclic AMP formation, and  
30           (e) inhibit PTH secretion;

2. The compound blocks increases in  $\text{Cl}^-$  current in *Xenopus* oocytes injected with p ly(A)-mRNA from bovine or

human parathyroid cells elicited by extracellular  $\text{Ca}^{2+}$ , but not in *Xenopus* oocytes injected with water; and

3. Similarly, the compound blocks a response in *Xenopus* oocytes, injected with cloned nucleic acid expressing the calcium receptor, elicited by extracellular  $\text{Ca}^{2+}$  or a calcimimetic compound (i.e., a compound able to mimic the effect of extracellular  $\text{Ca}^{2+}$ , including compounds potentiating the effect of extracellular  $\text{Ca}^{2+}$ ).

Calcium receptors are present in different cells. The pharmacological effects of the following cells, in response to extracellular  $\text{Ca}^{2+}$ , is consistent with the presence of a calcium receptor: parathyroid cell, bone osteoclast, juxtaglomerular kidney cell, proximal tubule kidney cell, distal tubule kidney cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct, keratinocyte in the epidermis, parafollicular cell in the thyroid (C-cell), intestinal cell, trophoblast in the placenta, platelet, vascular smooth muscle cell, cardiac atrial cell, gastrin-secreting cell, glucagon-secreting cell, kidney mesangial cell, mammary cell, endocrine and exocrine cells in the pancreas, fat/adipose cell, immune cell, GI tract cell, skin cell, adrenal cell, pituitary cell, hypothalamic cell and cell of the subfornical organ.

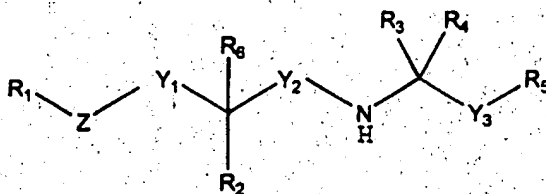
- The presence of a calcium receptor on the following cells have been confirmed using physical data, such as hybridization with nucleic acid encoding a calcium receptor: parathyroid cell, central nervous system cell, peripheral nervous system cell, cell of the thick ascending limb of Henle's loop and/or collecting duct in the kidney, parafollicular cell in the thyroid (C-cell), intestinal cell, GI tract cell, pituitary cell, hypothalamic cell, cell of the

subfornical organ, and endocrine and exocrine cells in the pancreas.

## II. $\alpha,\alpha$ -Disubstituted Arylalkylamine Derivatives

Structure I  $\alpha,\alpha$ -disubstituted arylalkylamine derivatives have the following chemical formula:

STRUCTURE I



where  $R_1$  is selected from the group consisting of: aryl, longer-length alk, and cycloalk. Preferably,  $R_1$  is either  
 10 optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted naphthyl, optionally substituted tetrahydronaphthyl, optionally substituted longer-length alkyl, optionally substituted  
 15 longer-length alkenyl or optionally substituted cycloalk.

More preferably,  $R_1$  is either an optionally substituted phenyl; an optionally substituted naphthyl; an optionally substituted pyridyl; an optionally substituted benzothiopyranyl; an optionally substituted carbazole;  
 20 unsubstituted longer-length alkyl; unsubstituted longer-length alkenyl; or monosubstituted longer-length alkyl or alkenyl, where the monosubstituent is either an optionally substituted phenyl or an optionally substituted cycloalkyl provided that the optionally substituted phenyl or optionally  
 25 substituted cycloalkyl can have one to four substituents each



independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH;

5        R<sub>2</sub> is selected from the group consisting of: lower alk, cycloalk, alkoxy, H, OH, =O, C(O)OH, C(O)O-lower alk, C(O)NH-lower alk, C(O)N(lower alk)<sub>2</sub>, SH, S-lower alk, NH<sub>2</sub>, NH-lower alk, and N(lower alk)<sub>2</sub>. More preferably, R<sub>2</sub> is OH or alkoxy, even more preferably, R<sub>2</sub> is OH or methoxy;

10        R<sub>3</sub> and R<sub>4</sub> is each independently lower alk or together cyclopropyl. Preferably, R<sub>3</sub> and R<sub>4</sub> are each independently a lower alkyl, more preferably, R<sub>3</sub> and R<sub>4</sub> are each independently methyl or ethyl;

      R<sub>5</sub> is aryl. Preferably, R<sub>5</sub> is either optionally  
15 substituted naphthyl or optionally substituted phenyl. More preferably, R<sub>5</sub> is substituted phenyl having a substituent in the meta or para position and optionally containing additional substituents;

      R<sub>6</sub> if present is either hydrogen, lower alkyl or lower  
20 alkenyl, wherein R<sub>6</sub> is not present if R<sub>2</sub> is =O. Preferably R<sub>6</sub> is either hydrogen or lower alkyl, more preferably R<sub>6</sub> is hydrogen.

      Y<sub>1</sub> is either covalent bond, alkylene, or alkenylene.  
Preferably, Y<sub>1</sub> is either covalent bond or lower alkylene.  
25 More preferably, Y<sub>1</sub> is methylene;

      Y<sub>2</sub> is alkylene. Preferably, Y<sub>2</sub> is lower alkylene. More preferably, Y<sub>2</sub> is methylene;

      Y<sub>3</sub> is alkylene. Preferably, Y<sub>3</sub> is lower alkylene. More preferably, Y<sub>3</sub> is methylene;

30        Z is selected from the group consisting of: covalent bond, O, S, NH, N-lower alk, alkylene, alkenylene, and alkynylene, provided that if Z is either O, S, NH, or N-lower alk, then Y<sub>1</sub> is not a covalent bond, further provided that Y<sub>1</sub>

and Z may together be a covalent bond. Preferably, Z is selected from the group consisting of: covalent bond, O, S, NH, N-lower alk, and alkylene. More preferably, Z is either O, S, lower alkylene, even more preferably, Z is O;

5 and pharmaceutically acceptable salts and complexes thereof.

"Alk" refers to either alkyl, alkenyl, or alkynyl.

"Lower alk" refers to either lower alkyl, lower alkenyl, or lower alkynyl, preferably, lower alkyl.

10 "Alkenyl" refers to an optionally substituted hydrocarbon group containing at least one carbon-carbon double bond between the carbon atoms and containing 2-15 carbon atoms joined together. The alkenyl hydrocarbon group may be straight-chain or contain one or more branches.

15 Branched- and straight-chain alkenyl preferably have 2 to 7 carbons, each of which may be optionally substituted.

Alkenyl substituents are each independently selected from the group consisting of: lower alkyl, lower alkenyl, halogen, alkoxy, lower haloalkyl, lower haloalkoxy, methylene dioxy, 20 unsubstituted aryl, unsubstituted cycloalkyl, OH, SH, CN, NO, NO<sub>2</sub>, NH<sub>2</sub>, CH=NNHC(O)NH<sub>2</sub>, CH=NNHC(S)NH<sub>2</sub>, CH<sub>2</sub>O-lower alkyl, C(O)lower alkyl, C(O)NH<sub>2</sub>, C(O)NH-lower alkyl, C(O)N(lower alkyl)<sub>2</sub>, C(O)OH, C(O)O-lower alkyl, NH-lower alkyl, N(lower alkyl)<sub>2</sub>, NHC(O)unsubstituted aryl, NHC(O)lower alkyl, N=N- 25 unsubstituted aryl, NHC(O)NH<sub>2</sub>, N(lower alkyl)C(O)lower alkyl, NHC(S)lower alkyl, N(lower alkyl)C(S)lower alkyl, NHS(O)lower alkyl, N(lower alkyl)S(O)lower alkyl, OC(O)lower alkyl, OCH<sub>2</sub>C(O)OH, OC(S)lower alkyl, S(O)lower alkyl, SC(O)lower alkyl, S-lower alkyl, S-lower haloalkyl, SO<sub>2</sub>-lower alkyl, SO<sub>2</sub>- 30 lower haloalkyl, S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH-lower alkyl, and S(O)<sub>2</sub>N(lower alkyl)<sub>2</sub>. Preferably, no more than three substituents are present. Even more preferably, the alkenyl

is a lower alkenyl, which is an unsubstituted branched- or straight-chain alkenyl having 2 to 4 carbons.

"Alkyl" refers to an optionally substituted hydrocarbon group joined by single carbon-carbon bonds and having 1-15 carbon atoms joined together. The alkyl hydrocarbon group may be straight-chain or contain one or more branches. Branched- and straight-chain alkyl preferably have 1 to 7 carbons, each of which may be optionally substituted. Alkyl substituents are each independently selected from the substituents described above for alkenyl. Preferably, no more than three substituents are present. More preferably, the alkyl is a lower alkyl, which is an unsubstituted branched- or straight-chain alkyl 1 to 4 carbons in length.

"Alkynyl" refers to an optionally substituted hydrocarbon group containing at least one carbon-carbon triple bond between the carbon atoms and containing 2-15 carbon atoms joined together. The alkynyl hydrocarbon group may be straight-chain or contain one or more branches. Branched- and straight-chain alkynyl preferably have 2 to 7 carbons, each of which may be optionally substituted. Alkynyl substituents are each independently selected from the substituents described above for alkenyl. Preferably, no more than three substituents are present. More preferably, the alkynyl is a lower alkynyl, which is an unsubstituted branched- or straight-chain alkynyl having 2 to 4 carbons.

"Alkenylene" refers to an optionally substituted hydrocarbon chain containing at least one carbon-carbon double bond between the carbon atoms. The alkenylene chain has 2 to 6 carbons and is attached at two locations to other functional groups or structural moieties. The alkenylene substituents are each independently selected from the substituents described above for alkenyl. Preferably, no

more than three substituents are present. More preferably, the alkenylene is a "lower alkenylene," which is an unsubstituted branched- or straight-chain alkenylene having 2 to 3 carbons.

- 5 "Alkoxy" refers to oxygen joined to an unsubstituted alkyl 1 to 12 carbon atoms in length, preferably 1 to 2 carbons in length. More preferably, the alkoxy is methoxy.

"Alkylene" refers to an optionally substituted hydrocarbon chain containing only carbon-carbon single bonds between the carbon atoms. The alkylene chain has 1 to 6  
10 carbons and is attached at two locations to other functional groups or structural moieties. The alkylene substituents are each independently selected from the substituents described above for alkenyl. Preferably, no more than three  
15 substituents are present. More preferably, the alkylene is a "lower alkylene," which is an unsubstituted branched- or straight-chain alkylene having 1 to 3 carbons.

"Alkynylene" refers to an optionally substituted hydrocarbon chain containing at least one carbon-carbon triple bond between the carbon atoms. The alkynylene chain  
20 has 2 to 6 carbons and is attached at two locations to other functional groups or structural moieties. The alkynylene substituents are each independently selected from the substituents described above for alkenyl. More preferably,  
25 the alkynylene is a "lower alkynylene," which is an unsubstituted branched- or straight-chain alkynylene having 2 to 3 carbons.

"Aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi- electron  
30 system, containing up to two conjugated or fused ring systems. Aryl includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally

substituted. Preferably, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted naphthyl, optionally substituted tetrahydronaphthyl.

Different substituents are preferred for the Structure I left hand  $R_1$  aryl and the Structure I  $R_2$  right hand aryl. Preferably, the aryl has no more than five independently selected substituents.

Preferably, when  $R_1$  is an aryl, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted naphthyl, or optionally substituted tetrahydronaphthyl. Preferred,  $R_1$  substituents are each independently selected from the group consisting of: unsubstituted alkyl, unsubstituted alkenyl, halogen, alkoxy, lower haloalkyl, lower haloalkoxy, methylene dioxy, unsubstituted aryl, unsubstituted cycloalkyl, OH, SH, CN, NO,  $\text{NO}_2$ ,  $\text{NH}_2$ , methylene dioxy,  $\text{CH}=\text{NNHC}(\text{O})\text{NH}_2$ ,  $\text{CH}=\text{NNHC}(\text{S})\text{NH}_2$ ,  $\text{CH}_2\text{O}$ -unsubstituted alkyl,  $\text{C}(\text{O})$ unsubstituted alkyl,  $\text{C}(\text{O})\text{NH}_2$ ,  $\text{C}(\text{O})\text{NH}$ -unsubstituted alkyl,  $\text{C}(\text{O})\text{N}$ (unsubstituted alkyl) $_2$ ,  $\text{C}(\text{O})\text{OH}$ ,  $\text{C}(\text{O})\text{O}$ -unsubstituted alkyl,  $\text{NH}$ -unsubstituted alkyl,  $\text{N}$ (unsubstituted alkyl) $_2$ ,  $\text{NHC}(\text{O})$ unsubstituted aryl,  $\text{NHC}(\text{O})$ unsubstituted alkyl,  $\text{N}=\text{N}$ -unsubstituted aryl,  $\text{NHC}(\text{O})\text{NH}_2$ ,  $\text{N}$ (unsubstituted alkyl) $\text{C}(\text{O})$ unsubstituted alkyl,  $\text{NHC}(\text{S})$ unsubstituted alkyl,  $\text{N}$ (unsubstituted alkyl) $\text{C}(\text{S})$ unsubstituted alkyl,  $\text{NHS}(\text{O})$ unsubstituted alkyl,  $\text{N}$ (unsubstituted alkyl) $\text{S}(\text{O})$ unsubstituted alkyl,  $\text{NS}(\text{O})$ , aryl,  $\text{OC}(\text{O})$ unsubstituted alkyl,  $\text{OCH}_2\text{C}(\text{O})\text{OH}$ ,  $\text{OC}(\text{S})$ unsubstituted alkyl,  $\text{S}(\text{O})$ unsubstituted alkyl,  $\text{SC}(\text{O})$ unsubstituted alkyl,  $\text{S}$ -unsubstituted alkyl,  $\text{S}$ -unsubstituted haloalkyl,  $\text{SO}_2$ -unsubstituted alkyl,

SO<sub>2</sub>-unsubstituted haloalkyl, S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH-unsubstituted alkyl, and S(O)<sub>2</sub>N(unsubstituted alkyl)<sub>2</sub>.

Preferred R<sub>1</sub> aryl substituents are each independently selected from the group consisting of: alkoxy, methylene dioxo, N(CH<sub>3</sub>)<sub>2</sub>, C(O)OCH<sub>3</sub>, phenyl, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH. More preferably, each R<sub>1</sub> aryl substituent is independently selected from the group consisting of: unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, lower haloalkoxy, CF<sub>3</sub>, F, Cl, Br, CN, and NO<sub>2</sub>.

In another preferred embodiment, R<sub>1</sub> is either 2-CN-phenyl, 2,3-dichloro phenyl, 2-nitro-phenyl, or 2-cyano-3-chloro-phenyl.

R<sub>2</sub> right hand aryl substituents are each independently selected from the substituents described above for alkenyl. In a preferred embodiment, the R<sub>2</sub> aryl substituents are each independently selected from the group consisting of: methoxy, lower alkyl, lower haloalkoxy, CFH<sub>2</sub>, CHF<sub>2</sub>, CF<sub>3</sub>, OCH<sub>2</sub>CF<sub>3</sub>, F, Cl, Br, I, OH, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, methylene dioxo, NH-lower alkyl, N(lower alkyl)<sub>2</sub>, C(O)lower alkyl, S-lower alkyl, S(O)lower alkyl, S(O)<sub>2</sub>lower alkyl, OC(O)lower alkyl, SC(O)lower alkyl, OC(S)lower alkyl, NHC(O)lower alkyl, N(lower alkyl)C(O)lower alkyl, NHC(S)lower alkyl, N(lower alkyl)C(S)lower alkyl, NHS(O)lower alkyl, N(lower alkyl)S(O)lower alkyl, C(O)OH, C(O)O-lower alkyl, C(O)NH<sub>2</sub>, C(O)NH-lower alkyl, C(O)N(lower alkyl)<sub>2</sub>, S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH-lower alkyl, and S(O)<sub>2</sub>N(lower alkyl)<sub>2</sub>.

In another preferred embodiment, R<sub>2</sub> aryl substituents are each independently selected from the group consisting of: methylene dioxo, methoxy, lower-haloalkyl, S-lower alkyl, lower-haloalkoxy, lower alkyl, halogen, SH, CN, OH, Cl, F, and Br. Preferred halogens are Cl, F, and Br.

"Carbocyclic aryl" refers to an aromatic ring or ring system having all carbon atoms. The carbon atoms are optionally substituted.

"Cycloalk" refers to an optionally substituted cyclic alkyl or an optionally substituted non-aromatic cyclic alkenyl and includes monocyclic and multiple ring structures such as bicyclic and tricyclic. The cycloalk has 3 to 15 carbon atoms, preferably, 5 to 12 carbon atoms. Optional substituents for the cycloalk are each independently selected from the group described above for alkenyl. Preferably, no more than three substituents are present. More preferably, the cycloalk is unsubstituted, even more preferably it is an unsubstituted cyclic alkyl. Preferred cycloalkyl groups include cyclohexyl and adamantyl.

"Haloalk" refers to substituted alkyl or substituted alkenyl, having no more than 4 carbons, where the substituents are halogens and at least one halogen is present. Preferably, the haloalk is an alkyl 1 to 3 carbons in length and the halogens are each independently either Cl or F, more preferably the alkyl has 2 carbons, more preferably the haloalkyl is a lower haloalkyl which has 1 carbon.

"Heterocyclic aryl" refers to an aryl having 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Examples of heterocyclic aryl include indolyl, pyridyl, quinolinyl, and isoquinolinyl.

"Longer-length alk" refers to either longer-length alkyl, longer-length alkenyl, or longer-length alkynyl; preferably, longer-length alkyl or longer-length alkenyl. More preferably a longer-length alk is 4 to 20 carbon atoms.

"Longer-length alkenyl" refers to an optionally substituted hydrocarbon group containing at least one carbon-carbon double bond between the carbon atoms, and which contains 2-20 carbon atoms joined together. Preferably, the longer-length alkenyl is 4 to 20 carbon atoms. The longer-length alkenyl hydrocarbon group may be straight-chain or contain one or more branches. Longer-length alkenyl substituents are each independently selected from the alkenyl substituent list described above. Preferably, the longer-length alkenyl is either unsubstituted or has one cycloalk or phenyl substituent. More preferably, the cycloalk substituent, if present, is unsubstituted, and more preferably the cycloalk substituent, if present, is either cyclohexyl or adamantyl.

15 "Longer-length alkyl" refers to an optionally substituted hydrocarbon group joined by single carbon-carbon bonds and which contains 1-20 carbon atoms joined together. Preferably, the longer-length alkyl is 4 to 20 carbon atoms. The longer-length alkyl hydrocarbon group may be 20 straight-chain or contain one or more branches. Longer-length alkyl substituents are each independently selected from the alkenyl substituent list described above. Preferably, the longer-length alkyl is either unsubstituted or has one cycloalk or phenyl substituent. More preferably, 25 the cycloalk substituent, if present, is unsubstituted, and more preferably the cycloalk substituent, if present, is either cyclohexyl or adamantyl.

"Longer-length alkynyl" refers to an optionally substituted hydrocarbon group containing at least one 30 carbon-carbon triple bond between the carbon atoms, and which contains 2-20 carbon atoms joined together. Preferably, the longer-length alkynyl is 4 to 20 carbon atoms. The longer-



length alkynyl hydrocarbon group may be straight-chain or contain one or more branches. Longer-length alkynyl substituents are each independently selected from the alkenyl substituent list described above. Preferably, the longer-length alkynyl is either unsubstituted or has one cycloalk or phenyl substituent substituent. More preferably, the cycloalk substituent, if present, is unsubstituted, and more preferably the cycloalk substituent, if present, is either cyclohexyl or adamantyl.

10 "Haloalkoxy" refers to oxygen joined to a "haloalk." Preferably, the haloalkoxy is a "lower-haloalkoxy," which is an oxygen joined to a lower-haloalkyl.

A.  $\alpha,\alpha$ -Disubstituted  $\beta$ -Phenethylamine Derivatives

More preferred calcilytic compounds are Structure I derivatives where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $Z$ ,  $Y_1$  and  $Y_2$  are as described above for Structure I  $\alpha,\alpha$ -disubstituted arylalkylamine derivatives, including preferred groups (see, Section II, *supra*); and

$R_5$  is either phenyl substituted with one to four independently selected substituents or an optionally substituted naphthyl having up to four independently selected substituents.  $R_5$  substituents are provided in Section II, *supra*, including preferred embodiments. More preferably  $R_5$  is either a substituted phenyl comprising a substituent in a meta or para position, more preferably, the substituent present in a meta or para position is either methyl, ethyl, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy.

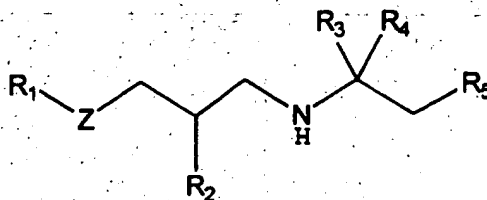
The activity of different calcilytic compounds was measured using the Calcium Receptor Assay described below. Examples of compounds having an  $IC_{50} \leq 50 \mu M$  include compounds 1, 9, 17, 25, 29, 42, 56, 79, 90, 101 and 164; examples of

preferred compounds having an  $IC_{50} < 10 \mu M$  include compounds 2, 3, 7, 8, 26, 27, 32, 33, 35, 37, 39, 41, 45, 48, 49, 59, 61, 66, 68, 71, 75, 93, 98, 103, 104, 110, 111, 114, 123, 124, 125, 128, 132, 144, 147, 152, 155, 158, 161, 162, 169 and 170; and examples of more preferred compounds having an  $IC_{50} < 1 \mu M$  include compounds 5, 6, 19, 20, 21, 28, 38, 40, 43, 44, 46, 47, 50, 51, 63, 64, 65, 67, 69, 72, 74, 96, 105, 106, 109, 112, 113, 115, 116, 117, 118, 119, 120, 121, 122, 126, 127, 129, 130, 131, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 145, 146, 148, 149, 150, 151, 153, 154, 156, 157, 159, 160, 163, 166, 167, and 168.

#### B. Structure II Compounds

Structure II compounds have the following structure:

Structure II



15

In one embodiment  $R_1$ ,  $R_2$ ,  $R_3$ , and  $R_4$  are as described above for Structure I  $\alpha, \alpha$ -disubstituted arylalkylamine derivatives, including preferred groups (see, Section II, *supra*); and

20  $R_5$  is either an optionally substituted naphthyl having one to four substituents independently selected from the group consisting of methyl, ethyl, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy, preferably the naphthyl is unsubstituted; or a substituted phenyl having one to four

substituent with at least one substituent in a meta or para position selected from the group consisting of: lower alkyl, methoxy, Cl, F, Br, and lower haloalkoxy, more preferably a methoxy is present in the para or meta position; even more  
5 preferably, the remaining R<sub>2</sub> substituents are independently selected from the group consisting of: methoxy, lower-haloalkyl, S-lower alkyl, lower-haloalkoxy, lower alkyl, halogen, SH, CN, OH, Cl, F, and Br.

provided that R<sub>1</sub> is not 6-CN-2-pyridyl; and

10 further provided that if R<sub>2</sub> is 3,4 dimethoxy-phenyl, then R<sub>1</sub> is not CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>O-phenyl; 2-cyclopentyl-phenyl; 2-Cl-phenyl; 2-CN-phenyl; 2-(3-furanyl)phenyl; or 4-(1,2,-benzisothiazol); preferably, R<sub>2</sub> is not 3,4 dimethoxy phenyl;

further provided that if R<sub>2</sub> is 4-methoxy-phenyl, then R<sub>1</sub>  
15 is not 2-cyclopentyl-phenyl; 2-CH<sub>3</sub>-phenyl; 2-benzyl-phenyl; 3-CH<sub>3</sub>, 4-CH<sub>3</sub>SO<sub>2</sub>-phenyl; or 4-(1,2,-benzisothiazol);

further provided that if R<sub>2</sub> is 4-Cl-phenyl, then R<sub>1</sub> is not 2-CH<sub>3</sub>-phenyl, 5-iso-propyl-phenyl; 2-CH<sub>3</sub>-phenyl; 4-CH<sub>3</sub>-phenyl; phenyl; 2-Cl-phenyl; 4-Cl-phenyl; 2-methoxy,  
20 4-CH<sub>3</sub>CHCH<sub>3</sub>-phenyl; 3,4 CH<sub>3</sub>-phenyl; 2,4 CH<sub>3</sub>-phenyl; 2,3 CH<sub>3</sub>-phenyl; 2-iso-propyl, 5-CH<sub>3</sub>-phenyl; pridyl; or 1-imidazole; 4-(1,2,-benzisothiazol); preferably, R<sub>1</sub> is either not 4-Cl, or R<sub>1</sub> is 3,4 dichlorophenyl; and

further provided that if R<sub>2</sub> is 3,5, dimethyl, 4-methoxy-phenyl, then R<sub>1</sub> is not 4-CH<sub>3</sub>, 6-CN-2-pyridyl; or  
25 thiophenecarboxamide; preferably, R<sub>2</sub> is not 3,5, dimethyl, 4-methoxy-phenyl.

In another embodiment, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are as described above for Structure I  $\alpha,\alpha$ -disubstituted arylalkylamine  
30 derivatives, including preferred groups (see, Section II, *supra*);

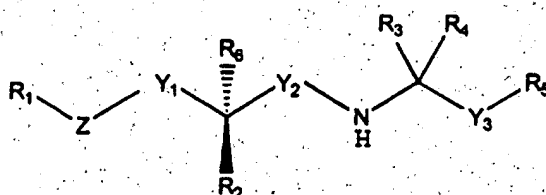
R<sub>5</sub> is either an optionally substituted naphthyl having one to four substituents independently selected from the

group consisting of methyl, ethyl, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, preferably the naphthyl is unsubstituted; or a substituted phenyl having one to four substituent with at least one substituent in a meta or para position selected from the group consisting of: methyl, ethyl, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, more preferably a methoxy is present in the para or meta position; even more preferably, the remaining  $R_1$  substituents are independently selected from the group consisting of: methoxy, lower-haloalkyl, S-lower alkyl, lower-haloalkoxy, lower alkyl, halogen, SH, CN, OH, Cl, F, and Br; and  $R_1$  is either 2-CN-phenyl, 2,3-dichloro phenyl, 2-nitro-phenyl, 2-cyano-3-chloro-phenyl, an optionally substituted pyridyl, an optionally substituted benzothiopyranyl, or an optionally substituted carbazole, where the optionally present substituents for the pyridyl, benzothiopyranyl, and carbazole as described in Section II supra, for aryl  $R_1$  substituents, including preferred substituents, and are even more preferably independently selected from the group consisting of: methoxy, lower-haloalkyl, S-lower alkyl, lower-haloalkoxy, lower alkyl, halogen, SH, CN, OH, Cl, F, and Br.

#### C. $R_2$ -group Stereochemistry

The different calcilytic compounds described herein can have different stereochemistry around different groups. In an embodiment of the present invention the Structure I compounds have the following absolute configuration structure with respect to  $R_2$ :

27



### III. Pharmaceutical Composition

The calcilytic compounds described herein can be formulated as a pharmaceutical composition to facilitate the administration of the compound to a patient. Preferred formulations contain a pharmaceutically acceptable carrier and a calcilytic compound as described in Section II, *supra.*, including the different embodiments.

Examples of suitable carriers are provided below, in Section V, "Administration," and include calcium carbonate, calcium phosphate, lactose, glucose, sucrose, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents.

### IV. TREATMENT OF DISEASES OR DISORDERS

Compounds inhibiting calcium receptor activity can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. Diseases or disorders which can be treated using a calcilytic compound are known in the art and can be identified using the present application as a guide. For example, diseases or disorders can be identified based on the functional responses of cells regulated by calcium receptor activity.

Diseases and disorders which can be treated using the calcilytic compounds described herein include those due to different cellular defects related to calcium receptor activity in different cells, such as a defective calcium

receptor or an abnormal number of calcium receptors; a defective intracellular protein acted on by a calcium receptor, or a defective protein or an abnormal number of proteins acting on a calcium receptor.

5        Functional responses of cells regulated by the calcium receptor are known in the art, including PTH secretion by parathyroid cells, calcitonin secretion by C-cells, bone resorption by osteoclasts, and  $\text{Ca}^{2+}$  secretion by kidney cells. Such functional responses are associated with different  
10        diseases or disorders.

For example, isolated osteoclasts respond to increases in the concentration of extracellular  $\text{Ca}^{2+}$  with corresponding increases in  $[\text{Ca}^{2+}]$ , arising partly from the mobilization of intracellular  $\text{Ca}^{2+}$ . Increases in  $[\text{Ca}^{2+}]$  in osteoclasts are  
15        associated with the inhibition of bone resorption.

Renin secretion from juxtaglomerular cells in the kidney is depressed by increased concentrations of extracellular  $\text{Ca}^{2+}$ . Extracellular  $\text{Ca}^{2+}$  causes the mobilization of intracellular  $\text{Ca}^{2+}$  in these cells. Other kidney cells respond  
20        to extracellular  $\text{Ca}^{2+}$  as follows: elevated  $\text{Ca}^{2+}$  inhibits formation of  $1,25(\text{OH})_2$ -vitamin D by proximal tubule cells, stimulates production of calcium-binding protein in distal tubule cells, and inhibits tubular reabsorption of  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  in the thick ascending limb of Henle's loop (MTAL), and  
25        reduces vasopressin action in the cortical collecting duct.

Other examples of functional responses affected by extracellular  $\text{Ca}^{2+}$  include promoting differentiation of intestinal goblet cells, mammary cells, and skin cells; inhibiting atrial natriuretic peptide secretion from cardiac  
30        atria; reducing cAMP accumulation in platelets; altering gastrin and glucagon secretion; acting on perivascular nerves to modify cell secretion of vasoactive factors; and affecting cells of the central nervous and peripheral nervous systems.

Diseases and disorders which might be treated or prevented, based upon the affected cells, include bone and mineral-related diseases or disorders; hypoparathyroidism; those of the central nervous system such as seizures, stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage, such as occurs in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, and Tourette's syndrome; diseases involving excess water reabsorption by the kidney, such as syndrome of inappropriate ADH secretion (SIADH), cirrhosis, congestive heart failure, and nephrosis; hypertension; preventing and/or decreasing renal toxicity from cationic antibiotics (e.g., aminoglycoside antibiotics); gut motility disorders such as diarrhea and spastic colon; GI ulcer diseases; GI diseases with excessive calcium absorption such as sarcoidosis; autoimmune diseases and organ transplant rejection; squamous cell carcinoma; and pancreatitis.

While calcilytic compounds of the present invention will typically be used to treat human patients, they may also be used to treat similar or identical diseases or disorders in other warm-blooded animal species, such as other primates, farm animals such as swine, cattle, and poultry; and sports animals and pets such as horses, dogs and cats.

Preferably, calcilytic compounds are used in the treatment of bone and mineral-related diseases or disorders. Bone and mineral-related diseases or disorders comprise a diverse class of disorders affecting nearly every major organ system in the body. Examples of bone and mineral-related diseases or disorders include osteosarcoma, periodontal

disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and osteoporosis. More preferably, calcilytic compounds are used to treat osteoporosis, a disease characterized by  
5 reduced bone density and an increased susceptibility to fractures. Osteoporosis is associated with aging, especially in women.

One way of treating osteoporosis is by altering PTH secretion. PTH can have a catabolic or an anabolic effect on  
10 bone. Whether PTH causes a catabolic effect or an anabolic effect seems to depend on how plasma levels of PTH are altered. When plasma levels of PTH are chronically elevated, as in hyperparathyroid states, there is a net loss of bone. In contrast, intermittent increases in plasma PTH levels, as  
15 achieved by administration of exogenous hormone, result in new bone formation. Anabolic action of PTH on bone is described, for example, by Dempster et al., *Endocrin. Rev.* 14:690-709, 1993.

As demonstrated by the Examples provided below,  
20 calcilytic compounds stimulate secretion of PTH. Such calcilytic compounds can be used to increase bone formation in a patient, for example, by intermittent dosing, thus achieving intermittent increases in the circulating levels of PTH.

## 25 V. ADMINISTRATION

The calcilytic compounds described by the present invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be  
30 found in Remington's Pharmaceutical Sciences, 18<sup>th</sup> ed., Mack Publishing Co., Easton, PA, 1990 (hereby incorporated by reference herein).



Suitable dosage forms, in part, depend upon the use or the route of entry, for example, oral, transdermal, transmucosal, or by injection (parenteral). Such dosage forms should allow the compound to reach a target cell whether the target cell is present in a multicellular host or in culture. For example, pharmacological compounds or compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and dosage forms which retard the compound or composition from exerting its effect.

Compounds can also be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

The pharmaceutically acceptable salt of the different compounds may be present as a complex. Examples of complexes include an 8-chlorotheophylline complex (analogous to, e.g., dimenhydrinate:diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained

from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see Remington's Pharmaceutical Sciences, 18<sup>th</sup> ed., Mack Publishing Co., Easton, PA, p. 1445, 1990. Such salts can be prepared using the appropriate corresponding bases.

Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free-base form of a compound is dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol in solution containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt is prepared by reacting the free base and acid in an organic solvent. (See, e.g., PCT/US92/03736, hereby incorporated by reference herein.)

Carriers or excipients can also be used to facilitate administration of the compound. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Examples of physiologically compatible solvents include sterile solutions of water for injection (WFI), saline solution and dextrose.

The calcilytic compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

The amounts of various calcilytic compounds to be administered can be determined by standard procedures taking

into account factors such as the compound  $IC_{50}$ ,  $EC_{50}$ , the biological half-life of the compound, the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art. Generally, it is an amount between about 0.1 and 50 mg/kg, preferably 0.01 and 20 mg/kg of the animal to be treated.

#### VI. Examples

The examples provided below, like the other examples provided herein, are not intended to limit the claimed invention, but rather illustrate different aspects and embodiments of the present invention.

##### EXAMPLE 1: Calcium Receptor Inhibitor Assay

This example illustrates the use of the Calcium Receptor Inhibitor Assay. Calcilytic activity was measured by determining the  $IC_{50}$  of the test compound for blocking increases of intracellular  $Ca^{2+}$  elicited by extracellular  $Ca^{2+}$  in HEK 293 4.0-7 cells stably expressing the human calcium receptor. HEK 293 4.0-7 cells were constructed as described by Rogers et al., *J. Bone Miner. Res.* 10 Suppl. 1:S483, 1995 (hereby incorporated by reference herein). Intracellular  $Ca^{2+}$  increases were elicited by increasing extracellular  $Ca^{2+}$  from 1 to 1.75 mM. Intracellular  $Ca^{2+}$  was measured using fluo-3, a fluorescent calcium indicator.

The procedure was as follows:

1. Cells were maintained in T-150 flasks in selection media (DMEM supplemented with 10% fetal bovine serum and 200  $\mu$ g/mL hygromycin B), under 5%  $CO_2$ :95% air at 37 °C and were grown up to 90% confluency.

2. The medium was decanted and the cell monolayer was washed twice with phosphate-buffered saline (PBS) kept at 37 °C. After the second wash, 6 mL of 0.02% EDTA in PBS was added and incubated for 4 minutes at 37 °C. Following the incubation, cells were dispersed by gentle agitation.

3. Cells from 2 or 3 flasks were pooled and pelleted (100 x g). The cellular pellet was resuspended in 10-15 mL of SPF-PCB+ and pelleted again by centrifugation. This washing was done twice.

10 Sulfate- and phosphate-free parathyroid cell buffer (SPF-PCB) contains 20 mM Na-Hepes, pH 7.4, 126 mM NaCl, 5 mM KCl, and 1 mM MgCl<sub>2</sub>. SPF-PCB was made up and stored at 4 °C. On the day of use, SPF-PCB was supplemented with 1 mg/mL of D-glucose and 1 mM CaCl<sub>2</sub>, and then split into two fractions.  
15 To one fraction, bovine serum albumin (BSA; fraction V, ICN) was added at 5 mg/mL (SPF-PCB+). This buffer was used for washing, loading and maintaining the cells. The BSA-free fraction was used for diluting the cells in the cuvette for measurements of fluorescence.

20 4. The pellet was resuspended in 10 mL of SPF-PCB+ containing 2.2 µM fluo-3 (Molecular Probes) and incubated at room temperature for 35 minutes.

5. Following the incubation period, the cells were pelleted by centrifugation. The resulting pellet was washed with SPF-PCB+. After this washing, cells were resuspended in SPF-PCB+ at a density of 1-2 x 10<sup>6</sup> cells/mL.

6. For recording fluorescent signals, 300 µL of cell suspension were diluted in 1.2 mL of SPF buffer containing 1 mM CaCl<sub>2</sub>, and 1 mg/mL of D-glucose. Measurements of fluorescence were performed at 37 °C with constant stirring using a spectrofluorimeter. Excitation and emission wavelengths were measured at 485 and 535 nm, respectively.

To calibrate fluorescence signals, digitonin (5 mg/mL in ethanol) was added to obtain  $F_{max}$ , and the apparent  $F_{min}$  was determined by adding Tris-EGTA (2.5 M Tris-Base, 0.3 M EGTA).

The concentration of intracellular calcium was calculated using the following equation:

Intracellular calcium =  $(F - F_{min} / F_{max}) \times K_d$ ; where  $K_d = 400$  nM.

7. To determine the potential calcilytic activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular  $Ca^{2+}$  from 1 to 2 mM. Calcilytic compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular  $Ca^{2+}$  elicited by extracellular  $Ca^{2+}$ .

In general, those compounds having lower  $IC_{50}$  values in the Calcium Receptor Inhibitor Assay are more preferred compounds. Compounds having an  $IC_{50}$  greater than 50  $\mu M$  were considered to be inactive. Preferred compounds are those having an  $IC_{50}$  10-50  $\mu M$ , more preferred compounds have an  $IC_{50}$  1-10  $\mu M$ , and most preferred compounds have an  $IC_{50}$  less than 1  $\mu M$ .

Examples of compounds having an  $IC_{50}$  greater than 50  $\mu M$  include compounds 22, 24, 34, 36, 52, 53, 54, 55, 58, 60, 62, 70, 84, 92, 99, and 102.

## EXAMPLE 2: Adrenergic Receptor Activity

Structure I  $\alpha, \alpha$ -disubstituted arylalkylamine derivatives include compounds which have both calcilytic activity and  $\beta$ -adrenergic receptor activity. If desired,  $\beta$ -adrenergic activity can be reduced using appropriate functional groups and structural modifications. Modifications which can be carried out to reduce  $\beta$ -adrenergic receptor activity include using alternative R<sub>1</sub> groups and

using absolute stereochemistry opposite to that which occurs in active  $\beta$ -adrenergic receptor antagonists, which provides compounds corresponding to the R enantiomer when R<sub>2</sub> is OH.  $\beta$ -adrenergic receptor activity and binding to the  $\beta$ -adrenergic receptor can be measured using standard techniques. For example, see Riva et al., *Mol. Pharmacol.* 36:201-210, 1989.

In one embodiment of the present invention the calcilytic compounds have an  $IC_{50} \geq 1.0$  nM, at the  $\beta$ -adrenergic receptor as measured using the " $\beta$ -Adrenergic Receptor Binding Assay" described below. In other embodiments, using the  $\beta$ -Adrenergic Receptor Assay calcilytic compounds have an  $IC_{50} \geq 1.0$   $\mu$ M, and  $IC_{50} \geq 10.0$   $\mu$ M.

The " $\beta$ -Adrenergic Receptor Binding Assay" is carried out as follows: Incubations are performed in polypropylene reaction tubes in a 37 °C water bath. To each tube 50  $\mu$ L of test sample is added, followed by 300  $\mu$ L of assay buffer (50 mM Tris-HCl, pH 7.5), and 50  $\mu$ L of 20 nM [ $^3$ H]-dihydroalprenolol. The binding reaction is initiated by the addition of 100  $\mu$ L of 3.75 mg/mL well-washed rat cortex membranes in assay buffer, and allowed to incubate at 37 °C for 30 minutes. Non-specific binding is determined in the presence of 10  $\mu$ M alprenolol. The final concentration of reactants is: 2 nM [ $^3$ H]-dihydroalprenolol, and 75 mg/mL rat cortex membrane in a reaction volume of 0.5 mL.

The binding reaction is terminated by rapid filtration with ice-cold assay buffer onto GF/C filters (Brandel, Gaithersburg, MD) which have been soaked for 15 minutes in assay buffer. The reaction is first diluted with 3 mL of cold assay buffer (4 °C), then aspirated onto the filter followed by 3 x 3 mL washes. Filter disks are placed in 7-mL polypropylene scintillation vials with 5 mL of ScintiSafe 50% (Fisher Scientific, Pittsburgh, PA), and counted overnight.

EXAMPLE 3: Stimulation of PTH Secretion

This example illustrates the ability of different calcilytic compounds to exert a biological effect on PTH secretion. PTH secretion was determined using dissociated  
5 bovine parathyroid cells as described below for Compounds 32, 33, and 38. Compounds 32, 33, and 38 all stimulated PTH secretion with an  $EC_{50}$  of less than 10  $\mu$ M.

Stimulation of PTH secretion was assayed as follows:

Preparation of Dissociated Bovine Parathyroid Cells

10 Parathyroid cell buffer (PCB) contains (mM): NaCl, 126; KCl, 4;  $MgSO_4$ , 1;  $K_2HPO_4/KH_2PO_4$ , 0.7; Na-Hepes, pH 7.45, and variable amounts of  $CaCl_2$ , as specified (reagent grade). PCB was typically supplemented with bovine serum albumin (BSA fraction V; ICN Biomedicals, Inc., Costa Mesa, CA; catalog  
15 #81-003) and 1 mg/mL of D-glucose (reagent grade) as indicated. Percoll purification buffer was prepared immediately before use by mixing 8 mL of Percoll (Pharmacia LKB, Alameda, CA; catalog #17-0891-01) and 7 mL of a twice-concentrated PCB solution without phosphate and containing 2  
20 mM  $CaCl_2$ .

Parathyroid glands were obtained from calves within minutes of slaughter at an abattoir and shipped via overnight express on ice in PCB containing 1.25 mM  $CaCl_2$ . The glands were trimmed and minced in ice-cold PCB containing 1.25 mM  
25  $CaCl_2$ , 1 mg/mL of D-glucose, and 2% BSA. Dissociated cells were obtained by collagenase digestion by vigorously shaking the minced tissue at 37 °C in PCB containing 0.5 to 1.0% Collagenase P (Boehringer Mannheim, Indianapolis, IN; catalog #1249 002), 2 to 5 units of deoxyribonuclease (Sigma, St.  
30 Louis, MO; catalog #D-0876), 1 mg/mL of D-glucose, and 1.25 mM  $CaCl_2$  (reagent grade). The cell suspension was triturated



at 30 minute intervals using 25- and 10-mL pipettes as the minced tissue was digested and the cells were dispersed.

Cells were pooled at 1-hour intervals by filtering the cell suspension through a 250- $\mu$ m Nitex screen into 15-mL polystyrene centrifuge tubes and spinning at 100 x g for 5 minutes at 22 °C. The pooled cell pellet was resuspended in Percoll purification buffer and purified by centrifugation at 14,500 x g for 20 minutes at 4 °C. Dissociated parathyroid cells equilibrated within a buoyant density of 1.048-1.062 above a dense band of red blood cells and below a diffuse band that contains adipocytes, strands of collagen, and damaged cells.

The dissociated parathyroid cells were removed with a sterile pipette and washed 3 to 4 times under sterile conditions in a 1:1 mixture of Ham's F-12 and Dulbecco's modified Eagle's medium (F-12/DMEM, Sigma, St. Louis, MO; catalog #D 8900) supplemented with 0.5% BSA, 100 U/mL of penicillin, 100  $\mu$ g/mL of streptomycin (Gibco BRL, Grand Island, NY; catalog #15140-031), and 20  $\mu$ g/mL of gentamicin (Sigma, St. Louis, MO; catalog #G 1397).

The cells were finally resuspended in F-12/DMEM supplemented with lower antibiotic concentrations (10 U/mL of penicillin, 10  $\mu$ g/mL of streptomycin, and 4  $\mu$ g/mL of gentamicin). This latter medium lacks serum and contained ITS\* (insulin, transferrin, selenous acid, BSA, and linoleic acid; Collaborative Biomedical Products, Bedford, MA; catalog #40352).

Cells were incubated in T-75 flasks at 37 °C in a humid atmosphere of 5% CO<sub>2</sub> in air. Parathyroid cells were collected for use by decanting the flasks after 18 to 24 hours in primary culture. The concentrations of gentamicin and streptomycin used here are considerably below the EC<sub>50</sub> for

mobilization of intracellular calcium (150 and 600  $\mu$ M, respectively).

Measurement of Parathyroid Hormone (PTH) Secretion

Sulfate, phosphate-free parathyroid cell buffer (SPF-PCB) contains (mM): NaCl, 126; KCl, 5; MgCl<sub>2</sub>, 1; Na-Hepes, pH 7.45, and variable amounts of CaCl<sub>2</sub>, as specified (reagent grade). SPF-PCB was typically supplemented with bovine serum albumin (BSA fraction V; ICN Biomedicals, Inc., Costa Mesa, CA; catalog #81-003) and 1 mg/mL of D-glucose (reagent grade) as indicated.

Incubations were performed in triplicate in 12 x 75 mm polypropylene or polystyrene tubes to which were added 2.5  $\mu$ L of test compound. The tubes were kept on ice until the drug additions were completed, then were transferred to a water bath at 37 °C, and the reactions were initiated by the addition of 0.2 mL of a suspension of dissociated cells at a density of 1 to 2 million cells/mL in SPF-PCB containing 0.5 mM Ca<sup>2+</sup>, 1 mg/mL of D-glucose, and 0.1% BSA. Incubation was for 30 minutes and the reaction was terminated by placing the tubes on ice. Cells were pelleted by gentle centrifugation (500 x g for 10 minutes at 4 °C) and 0.1 mL of supernatant was removed and stored at -20 °C.

Amino-terminal bovine PTH was measured by radioimmunoassay (RIA) using goat anti-hPTH antiserum H<sub>2</sub>, HPLC-purified <sup>125</sup>I-hPTH (1-34) and bovine PTH (1-84) standards. Serial dilutions of bPTH standards (1,000 pg/25  $\mu$ L to 3.8 pg/25  $\mu$ L) were done in 50 mM Tris, pH 7.4, containing 0.5 mM Na azide and 2% bovine serum albumin (diluent). Standards and samples were incubated for 2-3 days at 4 °C in the presence of antiserum after which 1,500-2,000 cpm label/tube was added. After an additional incubation for 1 to 2 days at 4 °C, dextran-coated charcoal was added to separate bound vs.

free label. The contents of each tube were mixed and the charcoal was pelleted by centrifugation. The supernatants were decanted into 12 x 75 mm polystyrene tubes and counted in a Packard Cobra gamma counter.

5        Example 4: General Procedures for the Preparation of Calcilytic Compounds

The calcilytic compounds described by the present invention can be prepared using standard techniques. For example, an overall strategy for preparing preferred  
10 compounds described herein can be carried out as described in this section. The examples which follow illustrate the synthesis of specific compounds. Using the protocols described herein as a model, one of ordinary skill in the art can readily produce other Structure I compounds.

15        All reagents and solvents were obtained from commercial vendors. Starting materials (e.g., amines and epoxides) were synthesized using standard techniques and procedures. GC/EI-MS (Gas Chromatographic/Electron-Impact Mass Spectrometric) analyses were performed on HP-5890 Series II gas chromatographs equipped with HP-Ultra-2 or HP-5MS columns (30 mm x  
20 0.25 mm ID) and HP-5971 or HP-5972 Mass Selective Spectrometric Detectors (MSD's) were used. MPLC (Medium-Pressure Liquid Chromatography) separations were carried out on silica gel (400 mesh) using an FMI pump, ISCO UV-6  
25 detector (254 nm) and FOXY 200 fraction collector. HPLC (High Performance Liquid Chromatography) was performed using RAININ HP-XL pumps and Dynamix UV-1 detectors (254 nm).

Examples of specific separation conditions and details are given in the individual experimental descriptions  
30 provided in the examples below. Chiral HPLC separations were carried out using a Beckman System Gold HPLC and UV detector

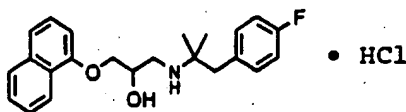
(254 nm) on Diacel® ChiralCel OD columns (Chiral Technologies, Inc., Exton, PA 19341).

NMR (Nuclear Magnetic Resonance) spectroscopy was performed on a Varian Gemini 300 spectrometer. Proton and carbon spectra were taken at 300 MHz and 75 MHz, respectively. NMR resonances are reported in ppm relative to tetramethylsilane (TMS) with the following descriptors for the observed multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) and m (multiplet).  $J_{AB}$  coupling constants are reported in Hz. Elemental analyses were performed and FT-IR data were acquired by Oneida Research Services, Inc., Whitesboro, NY 13492.

A general procedure used to synthesize many of the compounds was carried out as follows: A solution of glycidyl ether (i.e., 1,2-epoxy-3-phenoxypropane, 1 mmol) and excess amine (typically 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine, 1.5 mmol) in absolute ethanol (2 mL) is stirred overnight at 50-60 °C. The product is purified by one of three general methods: (1) conversion to the hydrochloride salt, followed by Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC, 0.1% HCl/acetonitrile); (2) conversion to the hydrochloride salt, followed by recrystallization from water-methanol or acetonitrile; and (3) purification by normal-phase chromatography (column chromatography or preparative, thin-layer chromatography (TLC)). Hydrochloride salts were also prepared by treatment of the corresponding free base in diethyl ether with 1M HCl (in diethyl ether).

EXAMPLE 5: Preparation of N-[2-Hydroxy-3-(1-

naphthoxy)propyl-1,1-dimethyl-2-(4-fluorophenyl)  
ethylamine Hydrochloride, Compound 2



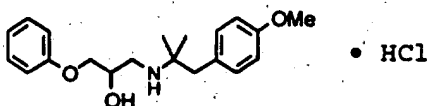
A stirred suspension of sodium hydride (4.0 g of 60% NaH  
5 in mineral oil, 100 mmol) in dimethylformamide (DMF, 100 ml)  
was treated with 1-naphthol (14.42 g, 100 mmol). After  
stirring for 1 hour at ambient temperature (room  
temperature), the reaction was treated with epichlorohydrin  
(10.18 g, 110 mmol) and stirred for 1 hour at 100 °C. The  
10 reaction was diluted with water and transferred to a  
separatory funnel using diethyl ether (500 ml). The organic  
phase was washed with 10% aqueous NaHCO<sub>3</sub> (3 x 200 ml), dried  
over anhydrous sodium sulfate, filtered, and concentrated.  
Kugelrohr distillation (~100 microns) yielded 1-naphthyl  
15 glycidyl ether as a clear, colorless oil: GC/EI-MS, m/z (rel.  
int.) 200 (M<sup>+</sup>, 61), 184 (1), 169 (5), 157 (12), 144 (79), 129  
(16), 115 (100), 101 (3), 89 (16).

A stirred solution of 1-naphthyl glycidyl ether (400 mg,  
2 mmol) and 1,1-dimethyl-2-(4-fluorophenyl)ethylamine (334  
20 mg, 2 mmol) in absolute ethanol (2 mL) was heated at 50-60 °C  
for 16 hours. Chromatography of the resulting reaction  
mixture through silica (5 x 30 cm) using a gradient of  
chloroform to 5% methanol in chloroform afforded the free  
base of the title compound: GC/EI-MS, m/z (rel. int.) 368  
25 (M<sup>+</sup>, 1), 352 (2), 258 (100), 183 (5), 157 (4), 127 (5), 115  
(18), 109 (23), 71 (30).

The free base in diethyl ether was treated with excess  
1M HCl (diethyl ether). The resulting solid was  
recrystallized from hot acetonitrile to afford 300 mg of the  
30 title compound as a crystalline solid: <sup>1</sup>H-NMR (DMF-D<sub>2</sub>) δ 9.9

(1H, br s), 9.5 (1H, br s), 8.33 (1H, d,  $J=9$ ), 7.91 (1H, d,  $J=9$ ), 7.57-7.50 (3H, m), 7.48-7.41 (3H, m), 7.19 (2H, t,  $J=10$ ), 7.03 (1H, d,  $J=7$ ), 6.37 (1H, br d,  $J=5$ ), 4.67 (1H, br s), 4.31 (2H, br t,  $J=6$ ), 3.61 (1H, br t), 3.42 (1H, br t),  
 5 3.31 (2H, s), 1.47 (3H, s), 1.46 (3H, s);  $^{13}\text{C}$ -NMR (DMF- $\text{D}_7$ )  $\delta$  161.5, 158.2, 152.2, 132.5, 130.8, 130.7, 129.7, 125.4, 124.4, 124.1, 124.5, 120.0, 118.3, 113.1, 112.8, 103.1, 68.1, 64.2, 57.9, 43.5, 40.3, 20.2.

EXAMPLE 6: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 3



A cooled (-78 °C) solution of diisopropylamine (65 g, 642 mmol) in tetrahydrofuran (THF, 800 mL) was treated with  
 15 244 mL of 2.5 M *n*-butyl lithium (610 mmol) in hexane. The reaction was stirred for 30 minutes at room temperature, cooled to -78 °C and treated dropwise with isobutyric acid (26.8 g, 305 mmol) and hexamethylphosphoramide (HMPA, 54.7 g, 305 mmol). The reaction was stirred for 30 minutes at room  
 20 temperature and treated with 4-methoxybenzyl chloride (43.4 g, 277 mmol). The reaction was stirred for 48 hours at room temperature and treated with 10% HCl (200 mL). The reaction was concentrated to 300 mL and diluted to 600 mL with water. The resulting solution was extracted with diethyl ether (2 x  
 25 300 mL) and the combined ether extracts were washed with 10% HCl (2 x 200 mL). The ether extract was then extracted with 1N NaOH (3 x 200 mL). The combined 1N NaOH washes were made acidic (pH 1) by the addition of concentrated HCl, and the resulting solution was extracted with diethyl ether (3 x 300

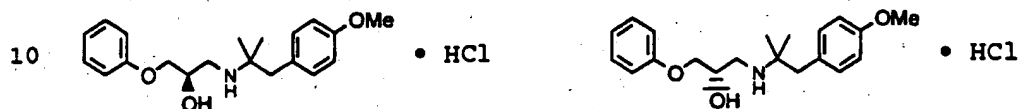
mL). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 32.6 g of 2,2-dimethyl-3-(4-methoxyphenyl)propionic acid as an oil: GC/EI-MS,  $m/z$  (rel. int.) 208 ( $M^+$ , 7), 121 (100), 91 (5),  
5 77 (6).

Triethylamine (16.8 g, 166 mmol) and 2,2-dimethyl-3-(4-methoxyphenyl)propionic acid (32.6 g, 157 mmol) were dissolved in 30 mL of water and enough acetone to maintain solubility at 0 °C. A solution of ethyl chloroformate (20.1  
10 g, 185 mmol) in acetone (100 mL) was then added dropwise. An aqueous solution (95 mL) of sodium azide (12.9 g, 198 mmol) was then added dropwise and the resulting reaction mixture stirred 45 minutes at room temperature. The intermediate acyl azide was then extracted into toluene (200 mL). The  
15 organic extract was washed with water, dried over anhydrous magnesium sulfate, and heated at 100 °C until the evolution of nitrogen ceased (~45 min). The toluene was removed under vacuum and replaced with benzyl alcohol. The solution was then heated at 100 °C for 16 hours. The excess benzyl alcohol  
20 was removed under vacuum. The resulting benzyl carbamate was dissolved in absolute ethanol (200 mL) and reduced in the presence of palladium hydroxide (2 g) under 90 p.s.i. hydrogen for 4 hours at room temperature. The reaction was filtered and concentrated to a yellow oil. Vacuum  
25 distillation afforded 13.0 g of 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine as a clear, colorless oil: GC/EI-MS,  $m/z$  (rel. int.) 180 ( $M+1$ , 1), 164 (5), 121 (25), 91 (5), 78 (19), 58 (100).

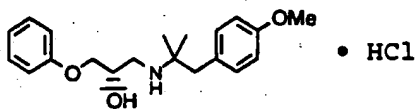
1,2-Epoxy-3-phenoxypropane (150 mg, 1 mmol) and 1,1-  
30 dimethyl-2-(4-methoxyphenyl)ethylamine (269 mg, 1.5 mmol) were used to prepare the free base of the title compound using the method of Example 5, *supra*. The hydrochloride salt was prepared by dilution of the reaction mixture with HCl (3

mmol) and water. Reversed-phase high-performance liquid chromatography (RP-HPLC, 0.1%/HCl to acetonitrile) of the resulting solution yielded 35 mg of the title compound as a white solid: GC/EI-MS,  $m/z$  (rel. int.) 314 (M-15, 1), 209 (19), 208 (100), 163 (6), 120 (19), 114 (7), 106 (6), 77 (12), 70 (9), 69 (15), 58 (6).

EXAMPLE 7: Resolution of the Enantiomers (R) or (S)-N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride. Compounds 32 and 33



Compound 32



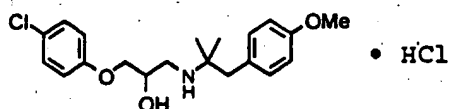
Compound 33

The enantiomers of (R) and (S)-N-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine hydrochloride (compounds 32 and 33) were obtained by chiral HPLC of the free base through ChiralCel OD (20 x 2.5 cm) using a combination of hexane-isopropanol containing 0.1% diethylamine (10 mL/min) measuring optical density at 260 nm. GC/EI-MS of each enantiomer gave  $m/z$  (rel. int.) 330 (M+1, 1), 314 (2), 208 (100), 183 (4), 163 (5), 121 (16), 77 (10), 70 (11). The hydrochloride of each enantiomer was prepared by treatment of the free base in diethyl ether with excess 1M HCl (diethyl ether). Evaporation of the solvent yielded the hydrochloride product as a solid.

EXAMPLE 8: Preparation of N-[2-Hydroxy-3-(4-chlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenylethyl)-amine Hydrochloride. Compound 5

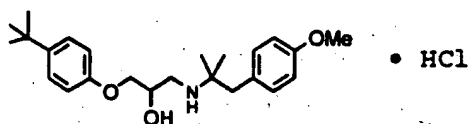


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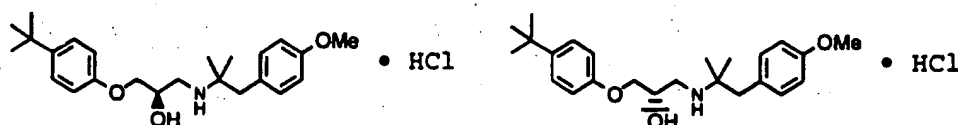
Using the method of Example 6, *supra*, 4-chlorophenyl glycidyl ether (185 mg, 1 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (269 mg, 1.5 mmol) were used to  
 5 prepare 272 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 348 (M-15, 1), 244 (35), 243 (15), 242 (100), 163 (9), 121 (24), 114 (7), 71 (24), 70 (26), 58 (15), 42 (7).

EXAMPLE 9: Preparation of N-[2-Hydroxy-3-(4-t-butylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 6  
 10



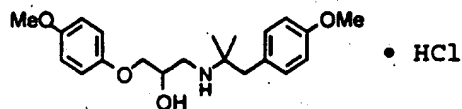
Using the method of Example 5, *supra*, 4-t-butylphenyl glycidyl ether (206 mg, 1 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (269 mg, 1.5 mmol) were used to  
 15 prepare the free base of the title compound. The hydrochloride was prepared by dilution of the reaction mixture with HCl (3 mmol) and water, which caused the product to precipitate. The mixture was heated to effect solution  
 20 and allowed to cool slowly to crystallize the product. The crystals were collected by filtration, washed with water/MeOH, and dried under vacuum to give 106 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 370 (M-15, 0.1), 265 (19), 264 (100), 163 (8), 121 (20), 114  
 25 (9), 91 (7), 71 (20), 70 (21), 58 (10), 57 (12).

Example 10: Resolution of the Enantiomers (R) and (S)-N-[2-Hydroxy-3-(4-t-butylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride. Compounds 20 and 21



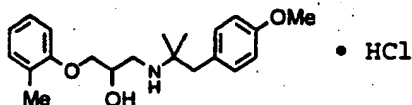
5        The enantiomers of (R) and (S)-N-[2-hydroxy-3-(4-t-butylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine hydrochloride were prepared using the method of Example 7, *supra*. GC/EI-MS of each enantiomer gave *m/z* (rel. int.) 386 (M<sup>+</sup>, 1), 370 (2), 264 (100), 163 (10), 135 (4), 121  
10 (36), 91 (8), 70 (11). The hydrochloride salt of each enantiomer was prepared by treatment of the corresponding free base in diethyl ether with excess 1M HCl (diethyl ether). Evaporation of the solvent yielded the corresponding hydrochloride product as a solid.

15        EXAMPLE 11: Preparation of N-[2-Hydroxy-3-(4-methoxyphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine Hydrochloride. Compound 7



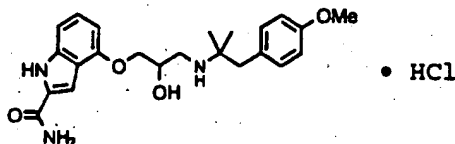
20        Using the method of Example 8, *supra*, 4-methoxyphenyl glycidyl ether (180 mg, 1 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (269 mg, 1.5 mmol) were used to prepare 231 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 344 (M-15, 0.1), 239 (17), 238 (100), 163 (9), 123 (7), 120 (17), 114 (6), 77 (5), 70 (13), 70 (11), 58  
25 (6).

EXAMPLE 12: Preparation of N-[2-Hydroxy-3-(2-methylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine Hydrochloride, Compound 8



5 Using the method of Example 9, *supra*, 2-methylphenyl glycidyl ether (164 mg, 1 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (269 mg, 1.5 mmol) were used to prepare 257 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 328 (M-15, 0.1), 223 (17), 222 (100), 163  
10 (8), 121 (23), 114 (11), 91 (13), 77 (6), 71 (19), 70 (21), 58 (11).

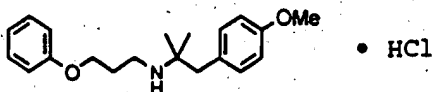
EXAMPLE 13: Preparation of N-[2-Hydroxy-3-(4-(2-carboxamido)indoloxo)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 9



15 Using the method of Example 6, *supra*, 4-glycidyloxy-2-indolecarboxamide (232 mg, 1 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (269 mg, 1.5 mmol) were used to prepare 222 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 396 (M-15, 0.1), 291 (17), 290 (100), 207  
20 (10), 158 (7), 130 (7), 121 (28), 114 (19), 71 (18), 70 (15).

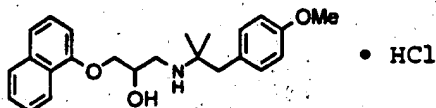
EXAMPLE 14: Preparation of N-(3-Phenoxypropyl)-

1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride  
Compound 17



To a stirred suspension of 50% KF-Celite (0.35 g, 3  
 5 mmol) in anhydrous acetonitrile (10 mL) was added 1,1-  
 dimethyl-2-(4-methoxyphenyl)ethylamine (0.27 g, 1.5 mmol) and  
 3-phenoxypropyl bromide (0.484 g, 2.25 mmol). The reaction  
 mixture was refluxed under nitrogen for 6 hours, followed by  
 stirring at room temperature for 62 hours. The mixture was  
 10 filtered and the filtrate, was evaporated. The hydrochloride  
 was prepared by dissolving the residue in HCl/methanol. The  
 resulting solution was concentrated and dried on a  
 lyophilizer. The residue was redissolved in dry methanol and  
 diluted with diethyl ether, which caused precipitation of 210  
 15 mg of the title compound as a white solid: GC/EI-MS,  $m/z$   
 (rel. int.) 298 (M-15, 2), 193 (15), 192 (100), 120 (13), 107  
 (5), 98 (9), 77 (8), 72 (7), 71 (8), 70 (6), 41 (4).

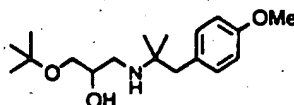
EXAMPLE 15: Preparation of N-[2-Hydroxy-3-(1-  
naphthoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
 20 Hydrochloride, Compound 19



Using the method of Example 5, *supra*, 1-naphthyl  
 glycidyl ether (1.0 g, 5 mmol) and 1,1-dimethyl-2-(4-  
 methoxyphenyl)ethylamine (1.0 mg, 5.6 mmol) were used to  
 25 prepare the free base of the title compound. Silica gel  
 chromatography of the reaction mixture using 5% methanol in  
 chloroform afforded 1.66 g (88%) of the purified product:

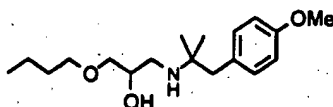
GC/EI-MS,  $m/z$  (rel. int.) 364 (M-15, 1), 258 (100), 183 (3), 163 (4), 144 (4), 121 (23), 115 (18), 71 (19);  $^1\text{H-NMR}$  ( $\text{C}_6\text{D}_6$ )  $\delta$  8.50 (1H, d,  $J=8.0$ ), 7.65 (1H, d,  $J=7.2$ ), 7.36-7.31 (3H, m), 7.21 (1H, t,  $J=7.9$ ), 6.98 (2H, d,  $J=8.6$ ), 6.71 (2H, d,  $J=8.6$ ), 6.62 (1H, d,  $J=7.7$ ), 4.08 (2H, m), 3.93 (1H, m), 3.32 (3H, s), 2.80 (1H, dd,  $J=11.6$  and 3.7), 2.71 (1H, dd,  $J=11.4$  and 6.4), 2.47 (2H, dd,  $J=13.3$  and 6.2), 0.94 (3H, s), 0.92 (3H, s);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  158.0, 154.3, 134.4, 131.2 (2 carbons), 129.9, 127.4, 126.3, 125.8, 125.2, 121.8, 120.5, 113.3 (2 carbons), 104.8, 70.4, 68.5, 55.0, 53.2, 46.4, 44.5, 26.9, 26.8. A portion of the free base in diethyl ether was treated with excess 1M HCl (diethyl ether). The resulting solid was recrystallized from hot acetonitrile to afford the title compound as a white solid.

15 EXAMPLE 16: Preparation of N-(2-Hydroxy-3-t-butoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.  
Compound 25



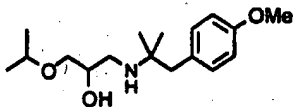
Using the method of Example 15, *supra*, *t*-butylglycidyl ether (142 mg, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to prepare 106 mg of the title compound as a clear, colorless oil: GC/EI-MS,  $m/z$  (rel. int.) 310 (M+1, 0.3), 294 (0.5), 222 (1.8), 188 (67.9), 163 (14.6), 132 (100), 121 (19.1);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.09 (2H, d,  $J=8.6$ ), 6.82 (2H, d,  $J=8.6$ ), 3.78 (3H, s), 3.68 (1H, m), 3.37 (2H, m), 2.27 (1H, dd,  $J=11.5$  and 4.2), 2.63 (3H, m), 1.19 (9H, s), 1.05 (3H, s), 1.03 (3H, s);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  156.0, 131.3, 130.3, 113.3, 72.9, 69.7, 64.5, 55.1, 52.9, 46.6, 44.7, 27.4, 26.9, 26.8.

EXAMPLE 17: Preparation of N-(2-Hydroxy-3-butoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.  
Compound 26



5        Using the method of Example 15, *supra*, *n*-butyl glycidyl ether (143  $\mu$ L, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to prepare 81 mg of the title compound as a clear, colorless oil; GC/EI-MS, *m/z* (rel. int.) 310 (*M*+1, 0.01), 174 (100),  
10 163 (19), 132 (18), 121 (31), 70 (20);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.03 (2H, d, *J*=8.6), 6.87 (2H, d, *J*=8.6), 3.74 (1H, m), 3.72 (3H, s), 3.40 (4H, m), 2.73 (3H, m), 2.59 (3H, m), 1.50 (2H, m), 1.30 (2H, m), 1.01 (3H, s), 0.99 (3H, s), 0.87 (3H, t, *J*=7.4);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  157.9, 131.2, 129.9, 113.2, 73.5, 71.2, 69.0,  
15 54.9, 53.1, 46.2, 44.5, 31.5, 26.6, 26.4, 19.1, 13.8.

EXAMPLE 18: Preparation of N-(2-Hydroxy-3-isopropoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.  
Compound 27

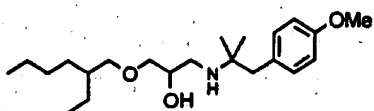


20        Using the method of Example 15, *supra*, isopropylglycidyl ether (126  $\mu$ L, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to prepare 53 mg of the title compound as a clear, colorless oil; GC/EI-MS, *m/z* (rel. int.) 296 (*M*+1, 0.2), 280 (1.4),  
25 222 (1.5), 174 (100), 132 (12), 121 (24);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.03 (2H, d, *J*=8.4), 6.77 (2H, d, *J*=8.4), 3.72 (3H, s), 3.70 (1H, m), 3.53 (1H, m), 3.38 (2H, m), 2.80 (1H, broad s), 2.73 (2H,

m), 2.58 (4H, m) 1.09 (6H, m), 1.01 (3H, s), 0.99 (3H, s);  
<sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ 157.9, 131.2, 129.9, 113.2, 73.4, 71.2, 69.0,  
 54.9, 53.1, 46.2, 44.5, 31.5, 26.6, 26.4, 19.1, 13.8.

EXAMPLE 19: Preparation of N-[2-Hydroxy-3-

5 (2-ethyl)hexanoxypopyll-1,1-dimethyl-2-(4-methoxyphenyl)-  
ethylamine. Compound 28

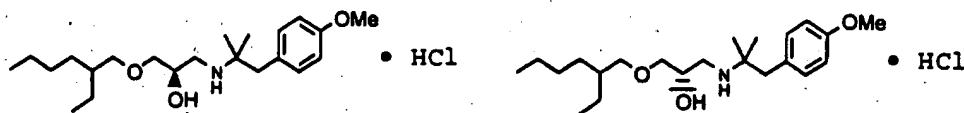


Using the method of Example 15, *supra*, 2-ethylhexyl  
 glycidyl ether (209 μL, 1.0 mmol) and 1,1-dimethyl-2-(4-  
 10 methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to  
 prepare 55 mg of the title compound as a clear, colorless  
 oil: GC/EI-MS, *m/z* (rel. int.) 366 (*M*+1, 0.2), 350 (1.1), 244  
 (100), 222 (2.5), 163 (8.7), 121 (15); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.06  
 (2H, d, *J*=8.5), 6.80 (2H, d, *J*=8.6), 3.75 (3H, s), 3.4 (2H,  
 15 d, *J*=5.3), 3.31 (2H, d, *J*=6.0), 2.88 (1H, broad), 2.78 (1H  
 dd, *J*=11.6 and 4.0), 2.62 (2H, m), 1.46 (1H, q, *J*=5.7), 1.24  
 (6H, m), 1.03 (4H, m), 0.84 (4H, m); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ 158.0,  
 131.3, 130.0, 113.3, 74.4, 73.7, 69.0, 55.1, 53.3, 46.3,  
 44.6, 39.5, 30.5, 29.0, 26.6, 26.4, 23.8, 23.0, 14.0, 11.0;  
 20 Anal. calculated for C<sub>22</sub>H<sub>33</sub>NO<sub>3</sub>: C, 72.3, H, 10.8, N, 3.8.  
 Found: C, 72.2, H, 9.9, N, 3.6.

EXAMPLE 20: Resolution of the Enantiomers (R) and

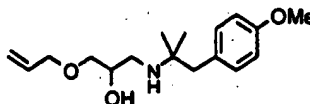
(S)-N-[2-Hydroxy-3-(2-ethyl)hexanoxypopyll-1,1-dimethyl-2-

(4-methoxyphenyl)ethylamine Hydrochloride, Compounds 63 and 64



The enantiomers (*R*) and (*S*)-*N*-[2-hydroxy-3-(2-ethyl)hexanoxypropyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine hydrochloride were prepared using the method of Example 7, *supra*. GC/EI-MS of each enantiomer gave *m/z* (rel. int.) 366 (*M*+1, 1), 350 (2), 244 (100), 222 (3), 163 (12), 133 (9), 121 (21), 115 (11), 100 (4), 71 (21). The hydrochloride salt of each enantiomer was prepared by treatment of the free amine in diethyl ether with excess 1M HCl (diethyl ether). Evaporation of the solvent yielded the hydrochloride product as a solid.

EXAMPLE 21: Preparation of *N*-(2-Hydroxy-3-allyloxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine. Compound 29

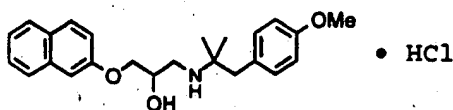


Using the method of Example 15, *supra*, allyl glycidyl ether (119  $\mu$ L, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to prepare 79 mg of the title compound as a clear, colorless oil: GC/EI-MS, *m/z* (rel. int.) 294 (*M*+1, 0.1), 278 (0.9), 222 (1.5), 172 (100), 163 (11), 121 (20);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.04 (2H, d, *J*=8.6), 6.79 (2H, d, *J*=8.6), 5.85 (1H, ddd, *J*=22.2, 10.5 and 5.7), 5.23 (1H, dd, *J*=17.3 and 1.5), 5.14 (1H, dd, *J*=10.3 and 1.5), 3.96 (2H, d, *J*=5.7), 3.74 (4H, m), 3.43 (2H,



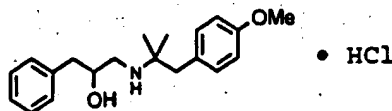
d,  $J=5.7$ ), 2.83 (1H, broad s), 2.77 (1H, dd,  $J=11.7$  and 4.1), 2.62 (5H, m), 1.02 (3H, s), 1.01 (3H, s);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  158.0, 134.5, 131.3, 129.9, 117.0, 113.3, 72.8, 72.2, 69.0, 55.0, 53.3, 46.3, 44.5, 26.6, 26.4.

5     EXAMPLE 22: Preparation of N-(2-Hydroxy-3-(2-naphthoxy)propyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride. Compound 35



Using the method of Example 4, *supra*, 2-naphthyl glycidyl ether (400 mg, 2 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (358 mg, 2 mmol) were used to prepare the free base of the title compound: GC/EI-MS,  $m/z$  (rel. int.) 364 (M-15, 1), 258 (100), 183 (2), 163 (3), 144 (4), 127 (10), 121 (22), 115 (20), 71 (11). The free base in diethyl ether was treated with excess 1M HCl (diethyl ether). The resulting solid was recrystallized from hot acetonitrile to afford 496 mg of the hydrochloride product as a white solid.

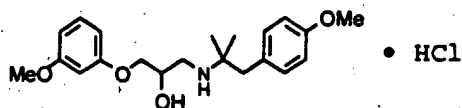
20     EXAMPLE 23: Preparation of N-(2-Hydroxy-3-phenylpropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride. Compound 37



Using the method of Example 6, *supra*, 2,3-epoxypropylbenzene (1 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.25 mmol) yielded 179 mg of the

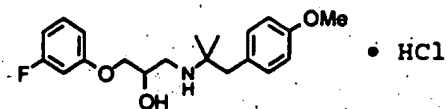
title compound as a white solid: GC/EI-MS,  $m/z$  (rel. int.)  
 298 (M-15, 1), 193 (16), 192 (100), 163 (7), 121 (18), 117  
 (12), 91 (32), 77 (5), 76 (5), 70 (16), 58 (9).

Example 24: Preparation of N-[2-Hydroxy-3-  
 5 (3-methoxyphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-  
ethylamine Hydrochloride, Compound 38



Using the method of Example 6, *supra*, 3-methoxyphenyl  
 glycidyl ether (1.5 mmol) and 1,1-dimethyl-2-(4-  
 10 methoxyphenyl)ethylamine (1.9 mmol) yielded 403 mg of the  
 title compound as a white solid: GC/EI-MS,  $m/z$  (rel. int.)  
 344 (M-15, 1), 239 (21), 238 (100), 163 (10), 121 (16), 114  
 (9), 106 (3), 77 (5), 71 (7), 70 (10), 58 (4).

EXAMPLE 25: Preparation of N-[2-Hydroxy-3-  
 15 (3-fluorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-  
ethylamine Hydrochloride, Compound 39

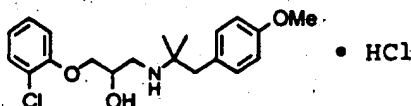


A solution of 3-fluorophenol (1.8 g, 16.1 mmol) in  
 acetone (100 mL) was treated with potassium carbonate (6.65  
 20 g, 48.2 mmol) and refluxed under nitrogen for 15 minutes.  
 Epibromohydrin (4.4 g, 32.1 mmol) was then added by syringe,  
 and the mixture was refluxed 3 hours. The mixture was cooled  
 and filtered, and the filtrate evaporated to dryness. The  
 residue was partitioned between ether/water, and the layers  
 25 separated. The ether layer was washed with saturated NaCl,

dried over sodium sulfate and evaporated. The resulting oil was distilled under vacuum to give 1.2 g of 3-fluorophenyl glycidyl ether.

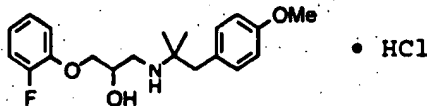
Using the method of Example 6, *supra*, 3-fluorophenyl glycidyl ether (1.5 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.9 mmol) yielded 398 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 332 (M-15, 1), 227 (22), 226 (100), 163 (7), 151 (6), 120 (22), 114 (6), 94 (7), 71 (11), 70 (16), 57 (8).

10 EXAMPLE 26: Preparation of N-[2-Hydroxy-3-(2-chlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine Hydrochloride, Compound 40



Using the method of Example 25, *supra*, 2-chlorophenyl glycidyl ether (1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.25 mmol) yielded 279 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 348 (M-15, 5), 245 (21), 244 (100), 242 (100), 163 (29), 121 (82), 114 (24), 77 (21), 71 (44), 70 (56), 58 (24).

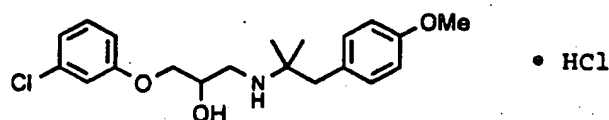
20 EXAMPLE 27: Preparation of N-[2-Hydroxy-3-(2-fluorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine Hydrochloride, Compound 41



Using the method of Example 25, *supra*, 2-fluorophenyl glycidyl ether (1.5 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.9 mmol) yielded 385 mg of the

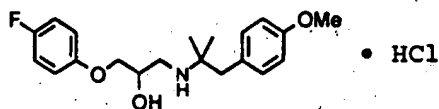
title compound as a white solid: GC/EI-MS,  $m/z$  (rel. int.)  
 332 (M-15, 2), 227 (20), 226 (100), 163 (4), 125 (3), 121  
 (15), 78 (4), 77 (4), 71 (7), 70 (9), 58 (3).

EXAMPLE 28: Preparation of N-[2-Hydroxy-3-(3-  
 5 chlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)  
ethylamine Hydrochloride, Compound 43



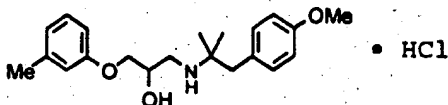
Using the method of Example 25, *supra*, 3-chlorophenyl  
 glycidyl ether (1.0 mmol) and 1,1-dimethyl-2-(4-  
 10 methoxyphenyl)ethylamine (1.25 mmol) yielded 168 mg of the  
 title compound as a white solid: GC/EI-MS,  $m/z$  (rel. int.)  
 348 (M-15, 0.9), 245 (7), 244 (35), 243 (25), 242 (100), 163  
 (7), 121 (22), 71 (11), 70 (16).

EXAMPLE 29: Preparation of N-[2-Hydroxy-3-  
 15 (4-fluorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)  
ethylamine Hydrochloride, Compound 44



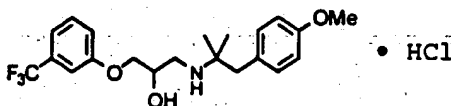
Using the method of Example 25, *supra*, 4-fluorophenyl  
 glycidyl ether (1.5 mmol) and 1,1-dimethyl-2-(4-  
 20 methoxyphenyl)ethylamine (1.9 mmol) yielded 398 mg of the  
 title compound as a white solid: GC/EI-MS,  $m/z$  (rel. int.)  
 332 (M-15, 1), 227 (20), 226 (100), 163 (5), 125 (4), 121  
 (15), 114 (3), 95 (4), 71 (8), 70 (10), 58 (5).

EXAMPLE 30: Preparation of N-[2-Hydroxy-3-(3-methylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 45



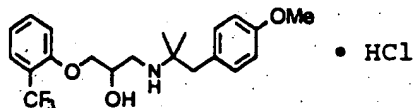
5 Using the method of Example 25, *supra*, 3-methylphenyl glycidyl ether (2.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (2.5 mmol) yielded 400 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 328 (M-15,1), 223 (16), 222 (100), 163 (5), 147 (5), 121  
10 (18), 114 (6), 91 (8), 76 (4), 71 (6), 70 (11).

EXAMPLE 31: Preparation of N-[2-Hydroxy-3-(3-trifluoromethylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 46



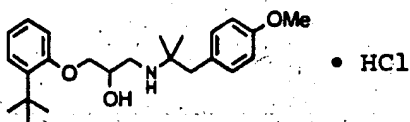
15 Using the method of Example 25, *supra*, 3-trifluoromethylphenyl glycidyl ether (2.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (2.5 mmol) yielded 600 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 382 (M-15, 1), 277 (16), 276 (100), 163 (7), 126  
20 (4), 121 (18), 114 (5), 96 (6), 71 (8), 70 (15), 57 (4).

EXAMPLE 32: Preparation of N-[2-Hydroxy-3-(2-trifluoromethylphenoxy)propyl]-1,1-dimethyl-2-(4-

methoxyphenyl)ethylamine Hydrochloride, Compound 47

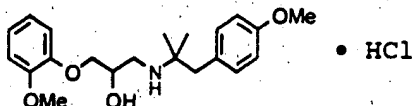
Using the method of Example 25, *supra*, 2-tri-  
fluoromethylphenyl glycidyl ether (2.0 mmol) and 1,1-  
5 dimethyl-2-(4-methoxyphenyl)ethylamine (2.5 mmol) yielded 690  
mg of the title compound as a white solid: GC/EI-MS, *m/z*  
(rel. int.) 382 (M-15, 1), 277 (16), 276 (100), 163 (10), 121  
(22), 114 (8), 96 (11), 71 (17), 70 (33), 58 (9), 42 (6).

EXAMPLE 33: Preparation of N-[2-Hydroxy-3-  
10 (2-*t*-butylphenoxy)propyl]-1,1-dimethyl-2-(4-  
methoxyphenyl)ethylamine Hydrochloride, Compound 48



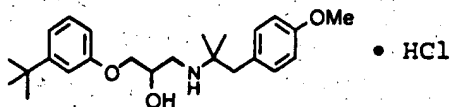
Using the method of Example 25, *supra*, 2-*t*-butylphenyl  
glycidyl ether (2.0 mmol) and 1,1-dimethyl-2-(4-  
15 methoxyphenyl)ethylamine (2.5 mmol) yielded 540 mg of the  
title compound as a white solid: GC/EI-MS, *m/z* (rel. int.)  
370 (M-15, 1), 265 (19), 264 (100), 163 (5), 121 (17), 114  
(6), 91 (8), 77 (3), 71 (9), 70 (8), 58 (3).

EXAMPLE 34: Preparation N-[2-Hydroxy-3-  
20 (2-methoxyphenoxy)propyl]-1,1-dimethyl-2-(4-

methoxyphenyl)ethylamine Hydrochloride, Compound 49

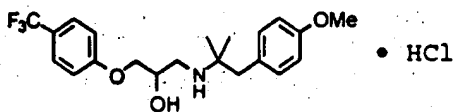
Using the method of Example 25, *supra*, 2-methoxyphenyl glycidyl ether (2.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (2.5 mmol) yielded 60 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 344 (M-15, 0.1), 239 (15), 238 (100), 163 (9), 122 (7), 121 (20), 114 (13), 77 (10), 71 (19), 70 (21), 58 (7).

EXAMPLE 35: Preparation of N-[2-Hydroxy-3-(3-  
 10 *t*-butylphenoxy)propyl]-1,1-dimethyl-2-(4-  
methoxyphenyl)ethylamine Hydrochloride, Compound 50



Using the method of Example 25, *supra*, 3-*t*-butylphenyl glycidyl ether (2.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (2.5 mmol) yielded 400 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 370 (M-15, 1), 265 (19), 264 (100), 163 (5), 121 (15), 114 (5), 110 (3), 91 (4), 71 (6), 70 (9), 57 (3).

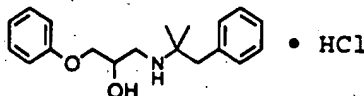
EXAMPLE 36: Preparation of N-[2-Hydroxy-3-(4-  
 20 trifluoromethylphenoxy)propyl]-1,1-dimethyl-2-(4-  
methoxyphenyl)ethylamine Hydrochloride, Compound 51



Using the method of Example 25, *supra*, 4-tri-fluoromethylphenyl glycidyl ether (1.43 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.8 mmol) yielded 270 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 382 (M-15, 3), 277 (35), 276 (100), 175 (8), 163 (8), 145 (16), 121 (34), 78 (9), 71 (15), 70 (19), 58 (8).

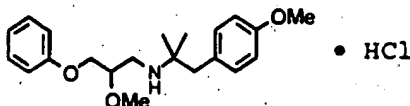
EXAMPLE 37: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-phenylethylamine Hydrochloride, Compound 56

10



Using the method of Example 5, *supra*, 1,2-epoxy-3-phenoxypropane (600 mg, 4 mmol) and 1,1-dimethyl-2-phenylethylamine (596 mg, 4 mmol) yielded the title compound: GC/EI-MS, *m/z* (rel. int.) 284 (M+1, 1), 208 (100), 162 (1), 133 (7), 91 (27), 77 (15), 70 (22). The free base in diethyl ether was treated with excess 1M HCl (diethyl ether). The resulting solid was recrystallized from hot acetonitrile to afford 596 mg of the hydrochloride product as a white solid.

20 EXAMPLE 38: Preparation of N-(2-Methoxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 59

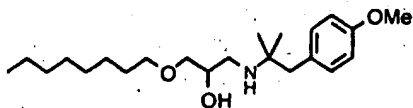


Allyl phenyl ether (1.34 g, 10 mmol) and N-bromosuccinimide (1.78 g, 10 mmol) were dissolved in 50 mL of methanol and stirred at room temperature for two days. The



product, a 1:1 mixture of 2-bromo-1-methoxy-3-phenoxypropane and 1-bromo-2-methoxy-3-phenoxypropane, was isolated by evaporating the methanol and dissolving the residue in heptane/ether/water. The organic layer was washed first with water, then brine, dried over sodium sulfate, and evaporated to dryness. The crude mixture (1.47 g, 6 mmol) was dissolved in 6 mL of acetonitrile, to which was added 50% KF-Celite (0.7 g, 12 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine (0.54 g, 3 mmole). The mixture was refluxed under nitrogen for 48 hours, and then cooled and filtered. The filtrate was evaporated to dryness, and the residue was taken up in water and ether. The ether layer was dried over sodium sulfate and concentrated to dryness. The residue was dissolved in 10 mL of diethyl ether and precipitated as the HCl salt by the addition of 10 mL of 1M HCl (diethyl ether). The collected solid was purified by RP-HPLC to yield 330 mg of the title compound as a white solid: GC/EI-MS,  $m/z$  (rel. int.) 328 (M-15, 5), 223 (43), 222 (100), 163 (9), 133 (13), 121 (42), 107 (13), 78 (11), 77 (23), 71 (12), 70 (32).

20      EXAMPLE 39: Preparation of N-(2-Hydroxy-3-octanoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.  
Compound 65

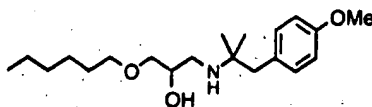


Using the method of Example 5, *supra*, 1-octyl glycidyl ether (187 mg, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to prepare 105 mg of the title compound as a clear, colorless oil: GC/EI-MS,  $m/z$  (rel. int.) 366 (M+1, 0.08), 350 (0.08), 244 (100), 222 (5.8), 163 (12), 121 (18):  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.08 (2H, d,

$J=8.6$ ), 6.82 (2H, d,  $J=8.6$ ), 3.79 (1H, m), 3.77 (3H, s), 3.45 (4H, m), 2.92 (1H, broad s), 2.79 (1H, dd,  $J=11.6$  and 4.1), 2.65 (2H, m), 2.55 (2H, m), 1.27 (8H, m), 1.06 (3H, s), 1.04 (3H, s), 0.88 (3H, t,  $J=6.7$ );  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  158.0, 131.2, 129.9, 113.2, 73.4, 71.6, 68.9, 55.0, 53.3, 46.2, 44.6, 31.7, 29.5, 29.3, 29.1, 26.5, 26.4, 26.0, 22.5, 14.0; FT-IR (film)  $\text{cm}^{-1}$  3409 (broad), 1611, 1512, 1245, 1120.

EXAMPLE 40: Preparation of N-(2-Hydroxy-3-hexanoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

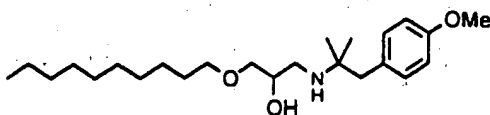
10 Compound 66



Using the method of Example 5, *supra*, 1-hexyl glycidyl ether (175 mg, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to prepare 95 mg of the title compound as a clear, colorless oil: GC/EI-MS,  $m/z$  (rel. int.) 216 (M-121), 163 (11), 121 (22), 114 (14);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.05 (2H, d,  $J=8.7$ ), 6.79 (2H, d,  $J=8.7$ ), 3.77 (1H, m), 3.75 (3H, s), 3.41 (4H, m), 2.97 (2H, broad), 2.79 (1H, dd,  $J=11.7$  and 4.1), 2.64 (3H, m), 1.52 (2H, m), 1.26 (6H, m), 1.04 (3H, s), 1.03 (3H, s), 0.85 (3H, t,  $J=6.7$ );  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  158.1, 131.3, 129.9, 113.4, 73.4, 71.7, 68.9, 55.1, 53.6, 46.3, 44.6, 31.6, 29.5, 26.5, 26.4, 25.7, 22.6, 14.0; FT-IR,  $\text{cm}^{-1}$  3405 (broad), 1611, 1512, 1245, 1116, 824.

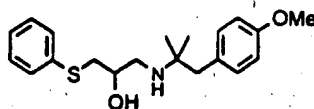
25 EXAMPLE 41: Preparation of N-(2-Hydroxy-3-decanoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.  
Compound 67

65



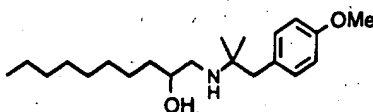
Using the method of Example 5, *supra*, 1-decyl glycidyl ether (235 mg, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to prepare 175 mg of the title compound as a clear, colorless oil: GC/EI-MS, *m/z* (rel. int.) 394 (*M*+1, 1), 378 (6), 273 (97), 272 (100), 222 (9), 163 (37), 121 (61); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.49 (2H, d, *J*=8.5), 6.82 (2H, d, *J*=8.5 Hz), 3.78 (3H, s), 3.75 (1H, m), 3.45 (4H, m), 2.80 (1H, dd, *J*=11.7 and 4.0), 2.77 (1H, broad s), 2.64 (4H, m), 1.56 (2H, m), 1.26 (16 H, m), 1.06 (3H, s), 1.05 (3H, s), 0.88 (3H, t, *J*=6.1); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ 158.1, 131.3, 130.0, 113.4, 73.5, 71.7, 69.1, 55.1, 53.3, 46.4, 44.6, 31.8, 29.6, 29.5, 29.4, 29.3, 26.7, 26.6, 26.1, 22.6, 14.1; FT-IR (film) cm<sup>-1</sup> 3115 (broad s), 1612, 1512, 1245, 1121, 824.

EXAMPLE 42: Preparation of N-(2-Hydroxy-3-thiophenylpropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.  
Compound 68



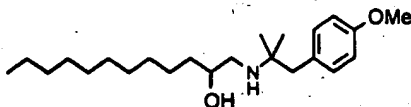
Using the method of Example 25, *supra*, phenyl glycidyl sulfide (3.9 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (4.9 mmol) yielded 194 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 330 (*M*-15, 4), 226 (21), 225 (58), 224 (100), 163 (25), 149 (25), 123 (100), 121 (75), 77 (18), 71 (22), 70 (26).

EXAMPLE 43: Preparation of N-(2-Hydroxydecanyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine. Compound 69



Using the method of Example 5, *supra*, 1,2-epoxydecane  
 5 (204 mg, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)-  
 ethylamine (197 mg, 1.1 mmol) were used to prepare 73 mg of  
 the title compound as a clear, colorless oil: GC/EI-MS, *m/z*  
 (rel. int.) 214 (M-121, 100), 196 (27.8), 163 (10), 121  
 (2.2); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.08 (2H, d, *J*=8.6), 6.83 (2H, d,  
 10 *J*=8.6), 3.79 (3H, s), 3.53 (1H, m), 2.79 (1H, dd, *J*=11.7 and  
 2.9), 2.67 (2H, s), 2.42 (1H, dd, *J*=12.6 and 9.6), 1.26 (18  
 H, m), 1.08 (3H, s), 0.88 (3H, t, *J*=6.6); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ  
 158.2, 131.4, 129.8, 113.5, 77.2, 69.8, 55.2, 53.8, 47.8,  
 46.5, 35.1, 31.9, 29.8, 29.7, 29.6, 29.3, 26.6, 26.4, 25.7,  
 15 22.7, 14.1; FT-IR (film) cm<sup>-1</sup> 3399 (broad s), 1612, 1512,  
 1246, 1039, 823.

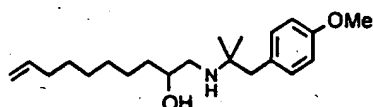
EXAMPLE 44: Preparation of N-(2-Hydroxydodecanyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine. Compound 70



Using the method of Example 5, *supra*, 1,2-epoxydodecane  
 20 (240 μL, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)-  
 ethylamine (197 mg, 1.1 mmol) were used to prepare 68 mg of  
 the title compound as a clear, colorless oil: GC/EI-MS, *m/z*  
 (rel. int.) 363 (M+1, 0.2), 348 (2), 242 (100), 224 (8), 163  
 25 (7), 121 (20); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.08 (2H, d, *J*=8.4), 6.83 (2H,  
 d, *J*=8.4), 3.79 (3H, s), 3.50 (1H, m), 2.78 (1H, dd, *J*=11.8  
 and 3.1), 2.66 (2H, s), 2.41 (1H, dd, *J*=11.5 and 9.3), 1.26

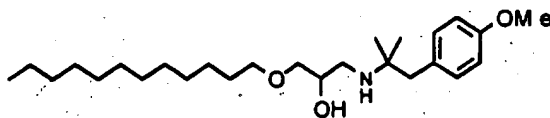
(18 H, m), 1.07 (6H, s), 0.88 (3H, t,  $J=6.5$ );  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  158.2, 131.4, 129.9, 113.4, 76.9, 70.0, 55.2, 53.6, 47.8, 46.6, 35.1, 31.9, 29.7, 29.6, 29.3, 26.7, 26.5, 25.7, 22.7, 14.1; FT-IR (film)  $\text{cm}^{-1}$  3386, 1612, 1512, 1246, 1039, 824.

5     EXAMPLE 45: Preparation of N-(2-Hydroxydec-9-enyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine. Compound 71



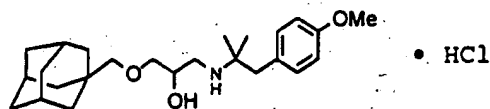
Using the method of Example 5, *supra*, 1,2-epoxy-9-decene (202 mg, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)-  
 10 ethylamine (197 mg, 1.1 mmol) were used to prepare 80 mg of the title compound as a clear, colorless oil: GC/EI-MS,  $m/z$  (rel. int.) 334 ( $M+1$ , 0.02), 318 (0.7), 212 (100), 194 (13), 163 (11), 121 (23);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.06 (2H, d,  $J=8.6$ ), 6.80 (2H, d,  $J=8.6$ ), 5.79 (1H, dddd,  $J=23.1$ , 10.2, 6.6 and 6.6),  
 15 4.95 (2H, m), 3.77 (3H, s), 3.52 (1H, m), 2.76 (1H, dd,  $J=11.7$  and 3.0), 2.64 (1H, s), 2.39 (1H, dd,  $J=11.6$  and 9.4), 2.03 (2H, m), 1.33 (10H, m), 1.05 (6H, s);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  158.1, 139.1, 131.4, 129.8, 114.1, 113.4, 69.8, 55.2, 53.7, 47.8, 46.5, 35.1, 33.8, 29.6, 29.0, 28.8, 26.6, 26.4, 25.7;  
 20 FT-IR (film)  $\text{cm}^{-1}$  3387 (broad, s), 1612, 1512, 1246, 1038, 910, 760.

25     EXAMPLE 46: Preparation of N-(3-Dodecanoxy-2-hydroxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine. Compound 72



Using the method of Example 5, *supra*, dodecyl glycidyl ether (242 mg, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to prepare 121 mg of the title compound as a clear, colorless oil: GC/EI-MS,  $m/z$  (rel. int.) 422 (M+1, 1), 406 (4), 300 (100), 222 (11), 163 (23), 121 (34);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.09 (2H, d,  $J=8.6$ ), 6.83 (2H, d,  $J=8.6$ ), 3.79 (3H, s), 3.76 (1H, m), 3.45 (4H, m), 2.81 (1H, dd,  $J=7.6$  and 4.0), 2.65 (4H, m), 1.53 (2H, m), 1.26 (20H, m), 1.06 (3H, s), 1.05 (3H, s), 0.88 (3H, t,  $J=6.4$ );  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  158.1, 131.3, 130.0, 113.4, 73.5, 71.7, 69.0, 55.1, 53.4, 46.4, 44.6, 31.9, 29.6, 29.4, 29.3, 26.7, 26.6, 26.1, 22.7, 14.1; FT-IR (film)  $\text{cm}^{-1}$  3415 (broad, s), 1612, 1512, 1246, 1121, 825.

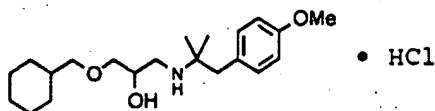
EXAMPLE 47: Preparation of N-[2-Hydroxy-3-(1-adamantylmethoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 74



Using the method of Example 9, *supra*, 1,2-epoxy-3-(1-adamantylmethoxy)propane (410 mg, 1.8 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (403 mg, 2.25 mmol) were used to prepare 625 mg of the title compound as a white solid: GC/EI-MS,  $m/z$  (rel. int.) 386 (M-15, 5), 281 (97), 280 (100), 163 (26), 149 (77), 135 (23), 121 (63), 107 (18), 93 (29), 79 (20), 71 (26).

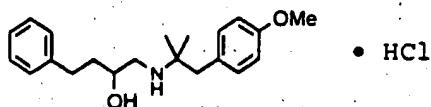
EXAMPLE 48: Preparation of N-(2-Hydroxy-3-cyclohexylmethoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 75

69



Using the method of Example 6, *supra*, 1,2-epoxy-3-cyclohexylmethoxypropane (212 mg, 1.2 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (279 mg, 1.6 mmol) were used to  
 5 prepare 200 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 334 (M-15, .1), 229 (15), 228 (100), 163 (9), 132 (5), 121 (16), 114 (9), 97 (7), 71 (8), 70 (9), 55 (16).

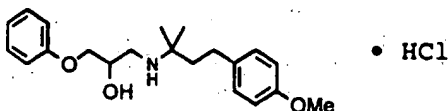
EXAMPLE 49: Preparation of N-(2-Hydroxy-4-phenylbutyl)-  
 10 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride.  
Compound 79



A solution of *m*-chloroperbenzoic acid (43.5 g, 151 mmol) in chloroform (250 ml) was treated with 4-phenyl-1-butene (20  
 15 g, 151 mmol). The reaction was stirred for 1 hour at room temperature and washed with sodium bicarbonate, sodium sulfite, and saturated sodium chloride. The solution was dried over sodium sulfate and evaporated to dryness to afford 3,4-epoxybutylbenzene (100%).

20 Using the method of Example 6, *supra*, 3,4-epoxybutylbenzene (1.4 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.7 mmol) were used to prepare 235 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 312 (M-15, 0.1), 207 (16), 206 (100), 163 (7),  
 25 131 (28), 121 (19), 91 (28), 77 (7), 71 (7), 70 (10), 58 (10).

EXAMPLE 50: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-3-(4-methoxyphenyl)propylamine Hydrochloride, Compound 90

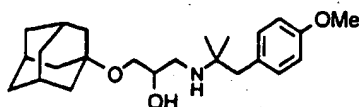


5        4-Methoxycinnamionitrile was hydrogenated in ethanol with palladium hydroxide on carbon to give 3-(4-methoxyphenyl)-propionitrile. A mixture of anhydrous cerium (III) chloride (1.99 g, 8.1 mmol) in dry THF (12 mL) was stirred for 3 hours at room temperature, cooled to -78 °C, and treated with MeLi  
10        (5.8 mL, 8.1 mmol). After stirring for 1 hour at -78 °C the reaction mixture was treated with 3-(4-methoxyphenyl)propionitrile (0.45 g, 2.8 mmol). The reaction mixture was stirred for 5 hours at -78 °C and then quenched with ammonium hydroxide. After warming to room temperature,  
15        the mixture was filtered, and the filtrate diluted with water and extracted with diethyl ether. The diethyl ether layer was dried over sodium sulfate and evaporated. The crude oil was purified by normal-phase chromatography to give 150 mg of 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine as a light yellow  
20        oil.

Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (0.62 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (0.78 mmol) were used to prepare 105 mg of the title compound as a white solid: GC/EI-MS, *m/z*  
25        (rel. int.) 343 (M<sup>+</sup>, 4), 209 (14), 208 (99), 161 (13), 122 (9), 121 (100), 77 (17), 72 (25), 71 (12), 70 (18), 58 (13).

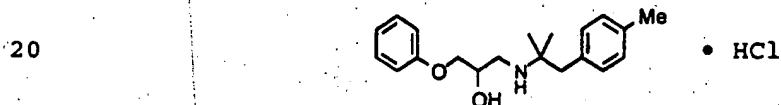


EXAMPLE 51: Preparation of N-[2-Hydroxy-3-(1-adamantanoxylpropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine, Compound 96



5 Using the method of Example 16, *supra*, 1-adamantyl glycidyl ether (350 mg, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (197 mg, 1.1 mmol) were used to prepare 207 mg of the title compound as a clear, colorless oil: GC/EI-MS, *m/z* (rel. int.) 338 (*M*+1, 0.1), 372 (0.3), 266  
 10 (65), 163 (1), 135 (100), 121 (16); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.02 (2H, d, *J*=8.3), 6.74 (2H, d, *J*=8.6), 3.70 (3H, s), 3.64 (1H, m), 3.38 (4H, m), 2.71 (1H, dd, *J*=11.5 and 4.0), 2.57 (3H, m), 2.06 (3H, broad s), 1.64 (6H, broad s), 1.53 (6H, m), 1.13 (4H, apparent t, *J*=6.9), 0.98 (3H, s), 0.97 (3H, s); <sup>13</sup>C-NMR  
 15 (CDCl<sub>3</sub>) δ 157.8, 131.2, 130.0, 113.1, 77.8, 70.5, 69.4, 54.9, 52.8, 46.3, 44.6, 32.0, 26.7, 26.6, 25.6, 23.9.

EXAMPLE 52: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-methylphenyl)ethylamine Hydrochloride, Compound 98



A solution of 2,4,6-triphenylpyrylium tetrafluoroborate (2.97 g, 7.5 mmol) in ethanol (15 mL) was treated with 4-methylbenzylamine (1 g, 8.25 mmol). The reaction was stirred overnight at room temperature and diluted with diethyl ether  
 25 to precipitate the product. The product was recrystallized from ethanol/diethyl ether to give 3.15 g of N-(4-

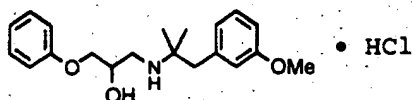
methylbenzyl)-2,4,6-triphenylpyridinium tetrafluoroborate as a tan solid.

Sodium hydride (0.92 g, 60% oil dispersion, 22.9 mmol) was added to methanol (10 mL) at 0 °C, followed by the  
5 addition of 2-nitropropane (2.04 g, 22.9 mmol). The reaction mixture was stirred for 30 minutes at room temperature and the methanol was evaporated at reduced pressure. A solution of the *N*-(4-methylbenzyl)-2,4,6-triphenylpyridinium tetrafluoroborate (3.15 g, 7.6 mmol) in DMSO (25 mL) was then  
10 added to the dry sodium salt of 2-nitropropane. The mixture was stirred at 60 °C overnight under nitrogen. The reaction was diluted with water, and the product extracted into diethyl ether. The ether layer was washed with saturated NaCl and dried over sodium sulfate. The ether solution was  
15 treated with Amberlyst 15 ion-exchange resin to absorb the 2,4,6-triphenylpyridine. The resin was filtered and the filtrate evaporated to yield 1.3 g of pure 1-(4-methylphenyl)-2-methyl-2-nitropropane.

The 1-(4-methylphenyl)-2-methyl-2-nitropropane (1.3 g)  
20 was hydrogenated for 5 hours at 65 p.s.i. hydrogen in ethanol (30 mL) using 1.4 g of Raney nickel as catalyst. Removal of the catalyst by filtration and evaporation of the solvent yielded 1.15 g of 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine as a clear oil.

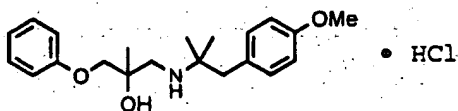
25 Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (1.3 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (0.6 mmol) were used to prepare 85 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 298 (M-15, 7), 209 (47), 208 (100), 114 (14), 107 (13),  
30 105 (46), 79 (12), 77 (28), 71 (18), 70 (31), 58 (13).

EXAMPLE 53: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(3-methoxyphenyl)ethylamine Hydrochloride, Compound 99



- 5 Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (200 mg, 1.3 mmol) and 1,1-dimethyl-2-(3-methoxyphenyl)ethylamine (263 mg, 1.5 mmol) were used to prepare 340 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 209 (14), 208 (100), 206 (6), 121 (11),  
 10 114 (5), 107 (5), 91 (6), 77 (12), 71 (8), 70 (16).

EXAMPLE 54: Preparation of N-(2-Hydroxy-2-methyl-3-phenoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 101



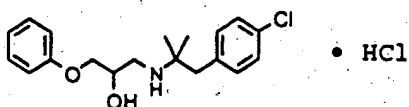
- 15 To a solution of 3-chloroperoxybenzoic acid (70% pure, 4.2 g, 17 mmol) in 40 mL of chloroform was added methallyl phenyl ether (2.5 g, 16.87 mmol). The mixture was stirred at room temperature for 5 hours then worked up by pouring into ether and sodium bicarbonate. The organic phase was washed  
 20 with sodium bisulfite, sodium bicarbonate, and sodium chloride, dried over anhydrous sodium sulfate and evaporated to give 2.3 g of 1,2-epoxy-2-methyl-3-phenoxypropane.

- Using the method of Example 6, *supra*, 1,2-epoxy-2-methyl-3-phenoxypropane (0.092 g, 0.56 mmol) and 1,1-  
 25 dimethyl-2-(4-methoxyphenyl)ethylamine (0.10 g, 0.56 mmol) were used to prepare 120 mg of the title compound as a white solid: GC/EI-MS, *m/z*, (rel. int.) 328 (M-15,1), 223 (15), 222

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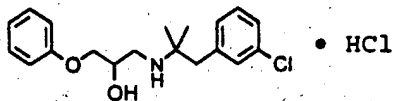
(100), 163 (13), 147 (13), 121 (21), 107 (11), 91 (9), 77 (13) 71 (12), 70 (49).

EXAMPLE 55: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-chlorophenyl)ethylamine Hydrochloride, Compound 103



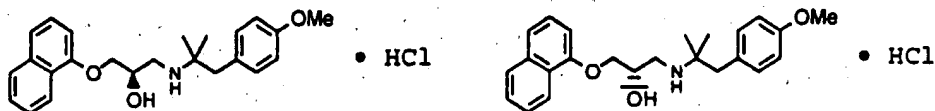
Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (950 mg, 6.3 mmol) and 1,1-dimethyl-2-(4-chlorophenyl)ethylamine (1.45 g, 7.9 mmol) were used to prepare 150 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 318 (M-15, 7), 209 (47), 208 (100), 127 (11), 125 (33), 114 (13), 107 (12), 77 (23), 71 (16), 70 (29), 58 (13).

EXAMPLE 56: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(3-chlorophenyl)ethylamine Hydrochloride, Compound 104



Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (1.3 g, 8.8 mmol) and 1,1-dimethyl-2-(4-chlorophenyl)ethylamine (2.0 g, 11 mmol) were used to prepare 338 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.) 318 (M-15, 1), 209 (14), 208 (100), 133 (4), 125 (12), 114 (6), 107 (6), 77 (10), 71 (8), 70 (15), 58 (5).

EXAMPLE 57: Resolution of the Enantiomers of (R)- and (S)- N-[2-Hydroxy-3-(1-naphthoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compounds 105 and 106



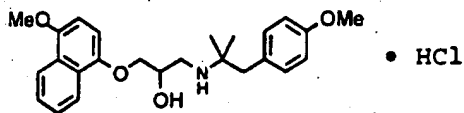
5                      Compound 105

Compound 106

The free base (1.5 g) of compound 19 was chromatographed through ChiralCel OD (20 x 2.5 cm) using ethanol-hexane (1:4, plus 0.1% diethylamine) at 10 mL/min (270 nm).

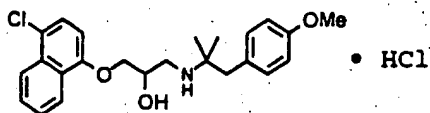
Chromatography of each enantiomer through Vydac C-18 (5 x 25  
10 cm) using a gradient of 0.1% HCl to acetonitrile (50 mL/min., 264 nm) afforded the hydrochloride salt of compound 105 (464 mg)  $[\alpha]_D^{25} = 15.3^\circ$  ( $c = 0.928$ ,  $\text{CHCl}_3$ ), m.p. 113-115°C and compound 106 (463 mg)  $[\alpha]_D^{25} = -13.8^\circ$  ( $c = 0.926$ ,  $\text{CHCl}_3$ ).

EXAMPLE 58: Preparation of N-[2-Hydroxy-3-(4-methoxy-(1-naphthoxy))propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 107



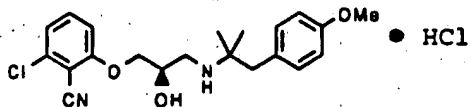
Using the method of Example 5, *supra*, 1,2-epoxy-3-[4-methoxy-(1-naphthoxy)]propane (462 mg, 2 mmol) and 1,1-  
20 dimethyl-2-(4-methoxyphenyl)ethylamine (120 mg, 0.67 mmol) yielded, after preparative TLC and RP-HPLC, 116 mg of the title compound as a white solid: GC/EI-MS,  $m/z$  (rel. int.) 394 (M-15, 2), 288 (100), 731 (11), 121 (15), 71 (22).

EXAMPLE 59: Preparation of N-[2-Hydroxy-3-(4-chloro-(1-naphthoxy))propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 108



- 5 Using the method of Example 5, *supra*, 1,2-epoxy-3-[4-chloro-(1-naphthoxy)]propane (469 mg, 2 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (120 mg, 0.67 mmol) yielded, after preparative TLC and RP-HPLC, 131 mg of the title compound as a white solid: GC/EI-MS, *m/z* (rel. int.)
- 10 414 (*M*<sup>+</sup>, 0.5), 398 (1), 292 (100), 121 (33), 71 (43).

EXAMPLE 60: Preparation of (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine Hydrochloride, Compound 109



- 15 To a solution of 18-crown-6 (3.96 g, 15 mmol) in 30 mL of acetonitrile were added dry potassium acetate (1.47 g, 15 mmol) and 2-chloro-6-fluorobenzonitrile (1.56 g, 10 mmol). The reaction was refluxed under nitrogen for 25 hours, then cooled to room temperature. Sodium hydroxide (2 mL of a 10 M
- 20 solution, 20 mmol) and water (5 mL) were added, and the reaction stirred at room temperature for two hours. The acetonitrile was removed on a rotary evaporator, and the residue was taken up in ether and water. The basic aqueous layer was washed three times with ether. The aqueous layer
- 25 was then made acidic with HCl, and the product extracted into ether. The ether layer was dried over anhydrous sodium

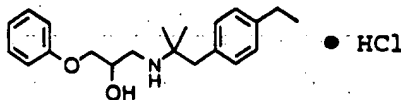
sulfate, filtered, and concentrated. The resulting solid was crystallized from water/methanol to yield 1.11 g of 3-chloro-2-cyanophenol.

3-Chloro-2-cyanophenol (0.55 g, 3.58 mmol) was dissolved in 10 mL of dimethylformamide, and the solution cooled to 0 °C. Sodium hydride (0.158 g, 3.94 mmol 60% in oil), washed with hexane and dimethylformamide, was added to cooled solution over a period of one minute. After stirring for 10 minutes at room temperature, (2R)-(-)-glycidyl 3-nitrobenzenesulfonate was added and stirred 16 hours. The reaction was poured into ether and dilute sodium hydroxide. The ether layer was separated and the aqueous layer extracted once more with ether. The combined ether extracts were washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give 0.7 g of (R)-3-chloro-2-cyanophenyl glycidyl ether.

Using the method of Example 6, *supra*, (R)-3-chloro-2-cyanophenyl glycidyl ether (0.7 g, 3.34 mmol) and 1,1-dimethyl-(4-methoxyphenyl)ethylamine (0.72 g, 4.0 mmol) were used to prepare 570 mg of the title compound as a white solid: <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.65 (1H, br s), 8.2 (1H, br s), 7.4 (1H, t), 7.15 (2H, d), 7.03 (1H, d), 6.95 (1H, d), 6.8 (2H, d), 4.8 (1H, m), 4.3 (2H, d), 3.75 (3H, s), 3.4 (2H, m), 3.13 (2H, dd), 1.44 (3H, s), 1.40 (3H, s); <sup>13</sup>C-NMR 161.9, 159.4, 138.2, 135.1, 132.4, 126.8, 122.8, 114.4, 114.2, 111.6, 104.0, 71.8, 66.0, 61.9, 55.8, 45.4, 43.9, 23.5, 23.3.

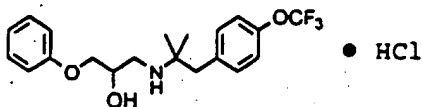
EXAMPLE 61: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-ethylphenyl)ethylamine Hydrochloride, Compound 110

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Using the method of Example 52, *supra*, 4-ethylbenzylamine (4.0 g, 29.6 mmol) was used to prepare 3.6 g of 1,1-dimethyl-2-(4-ethylphenyl)ethylamine. Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (0.43 g, 2.9 mmol) and 1,1-dimethyl-2-(4-ethylphenyl)ethylamine (0.5 g, 2.8 mmol) were used to prepare 600 mg of the title compound as a white solid: GC/EI-MS, *m/z*, (rel. int.) 313 (M-15, 1), 209 (23), 208 (100), 133 (5), 119 (12), 114 (6), 107 (5), 104 (7), 91 (6), 77 (10), 71 (8), 70 (12).

EXAMPLE 62: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-trifluoromethoxyphenyl)ethylamine Hydrochloride, Compound 111



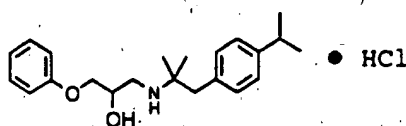
Using the method of Example 52, *supra*, 4-trifluoromethoxybenzylamine (2.0 g, 10.5 mmol) was used to prepare 2.2 g of 1,1-dimethyl-2-(4-trifluoromethoxyphenyl)ethylamine.

Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (0.12 g, 0.8 mmol) and 1,1-dimethyl-2-(4-trifluoromethoxyphenyl)ethylamine (0.175 g, 0.8 mmol) were used to prepare 15 mg of the title compound as a white solid: GC/EI-MS, *m/z*, (rel. int.) 368 (M-15, 2), 209 (39), 208 (100), 175 (20), 133 (5), 114 (5), 107 (6), 77 (11), 71 (7), 70 (12), 58 (5).

EXAMPLE 63: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-isopropylphenyl)ethylamine Hydrochloride, Compound 112

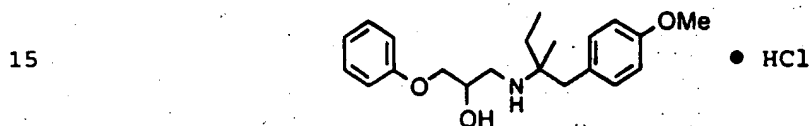


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Using the method of Example 52, *supra*,  
 4-isopropylbenzylamine (4.89 g, 32.8 mmol) was used to  
 prepare 4.1 g of 1,1-dimethyl-2-(4-isopropylphenyl)-  
 5 ethylamine. Using the method of Example 6, *supra*,  
 1,2-epoxy-3-phenoxypropane (0.173 g, 1.15 mmol) and  
 1,1-dimethyl-2-(4-isopropylphenyl)ethylamine (0.275 g, 1.44  
 mmol) were used to prepare 89 mg of the title compound as a  
 white solid: GC/EI-MS, *m/z*, (rel. int.) 326 (M-15,1), 209  
 10 (14), 208 (100), 133 (9), 117 (5), 114 (5), 105 (5), 91 (6),  
 77 (8), 71 (8), 70 (13), 58 (5).

EXAMPLE 64: Preparation of N-(2-Hydroxy-3-  
phenoxypropyl)-1-ethyl-1-methyl-2-(4-methoxyphenyl)ethanamine  
Hydrochloride. Compound 113



4-Hydroxybenzyl alcohol (0.35 g, 2.82 mmol) and  
 tetrabutylammonium fluoride (0.147 g, 0.56 mmol) were  
 dissolved in 3 mL of 2-nitrobutane and heated to 130-145 °C  
 under nitrogen for 20 hours. The reaction mixture was cooled  
 20 and partitioned between water and ether. The ether layer was  
 separated, washed with saturated brine, dried over anhydrous  
 sodium sulfate, and concentrated. The crude material was  
 purified by preparative TLC using ethyl acetate/hexane as the  
 elutant. The yield of 1-ethyl-1-methyl-2-(4-hydroxyphenyl)-  
 25 nitroethane was 0.21 grams.

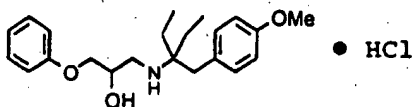
To a suspension of 40% (wt/wt) potassium fluoride on alumina (0.73 g, 5 mmol) in 3 mL of acetonitrile were added 1-ethyl-1-methyl-2-(4-hydroxyphenyl)nitroethane (0.21 g, 1.0 mmol) and iodomethane (0.21 g, 1.5 mmol). The reaction was stirred at room temperature for 4 days and then filtered and rinsed with acetonitrile. The acetonitrile was removed on a rotary evaporator, and the residue was partitioned between ether and water. The ether layer was separated, washed with sodium bisulfite, sodium carbonate, and saturated brine, then dried over anhydrous sodium sulfate and concentrated. The yield of 1-ethyl-1-methyl-2-(4-methoxyphenyl)nitroethane was 0.183 g.

Nickel chloride monohydrate (0.107 g, 0.404 mmol) was dissolved in 5 mL of methanol, followed by the addition of sodium borohydride (0.05 g, 1.2 mmol). After stirring for 5 minutes, 1-ethyl-1-methyl-2-(4-methoxyphenyl)nitroethane (0.18 g, 0.807 mmol) in 3 mL of methanol was added, and stirred for 5 minutes. Sodium borohydride (0.11 g, 2.83 mmol) was then added in portions over 5 minutes. The reaction was then stirred overnight under a hydrogen balloon. The reaction mixture was filtered, and the methanol was removed on a rotary evaporator. The residue was taken up in ether and dilute sodium hydroxide. The ether layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The yield of 1-ethyl-1-methyl-2-(4-methoxy-phenyl)ethylamine was 0.127 grams.

Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (0.086 g, 0.57 mmol) and 1-ethyl-1-methyl-2-(4-methoxyphenyl)ethylamine (0.11 g, 0.57 mmol) were used to prepare 90 mg of the title compound as a white solid: GC/EI-MS, *m/z*, (rel. int.) 314 (M-29,2), 223 (15), 222 (100),

128 (6), 121 (20), 107 (5), 84 (10), 78 (5), 77 (12), 72 (5),  
56 (7).

EXAMPLE 65: Preparation of N-(2-Hydroxy-3-  
phenoxypropyl)-1,1-diethyl-2-(4-methoxyphenyl)ethylamine  
5 Hydrochloride, Compound 114



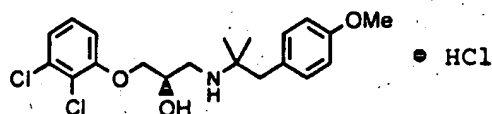
Anhydrous cerium (III) chloride (13.6 g, 55.2 mmol) was  
suspended in 80 mL of dry tetrahydrofuran, and stirred under  
nitrogen for 16 hours. This suspension was cooled in an ice  
10 bath, and ethylmagnesium chloride (27.6 mL, 55.18 mmol, 2 M  
solution in tetrahydrofuran) was added over 5 minutes. After  
stirring for 1 hour, methyl 4-methoxyphenylacetate (3.98 g,  
22.07 mmol) was added to the suspension and stirred for  
another 2 hours. The reaction was then partitioned between  
15 ether and saturated ammonium chloride. The ether layer was  
separated, washed with dilute HCl, water, and saturated  
brine, dried over anhydrous sodium sulfate, and concentrated.  
The yield of 1,1-diethyl-2-(4-methoxyphenyl)ethanol was 4.65  
g.

20 Powdered sodium cyanide (1.18 g, 24 mmol) was placed in  
a flask and covered with 5.5 mL of acetic acid. A mixture of  
sulfuric acid (3 mL) and acetic acid (2.75 mL) was cooled to  
0 °C and then added to the cyanide suspension over a period  
of 3 minutes. The mixture was stirred for 30 minutes at room  
25 temperature, followed by the addition of 1,1-diethyl-2-(4-  
methoxyphenyl)ethanol (4.6 g, 22 mmol). The mixture was  
stirred overnight then poured into ice and sodium hydroxide.  
The product was extracted with ether, and the ether layer  
dried over anhydrous sodium sulfate, and concentrated. The

residue was suspended in 20% sodium hydroxide and refluxed overnight under nitrogen. The reaction was cooled, diluted with water, and extracted with ether. The ether layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by reversed-phase HPLC (C-18 using 0.1% HCl/acetonitrile as the elutant) to give 1.91 g of 1,1-diethyl-2-(4-methoxyphenyl)ethylamine.

Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (0.15 g, 1.0 mmol) and 1,1-diethyl-2-(4-methoxyphenyl)ethylamine (0.249 g, 1.2 mmol) were used to prepare 244 mg of the title compound as a white solid: GC/EI-MS, *m/z*, (rel. int.) 328 (M-29,6), 237 (17), 236 (100), 121 (22), 106 (5), 98 (7), 78 (5), 77 (11), 70 (7), 56 (5).

EXAMPLE 66: Preparation of (R)-N-[2-Hydroxy-3-(2,3-dichlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride. Compound 115

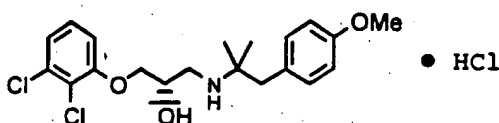


2,3-Dichlorophenol (0.69 g, 4.24 mmol) was dissolved in 15 mL of acetone, followed by the addition of powdered potassium carbonate (1.6 g, 11.57 mmol). This mixture was stirred for 2 hours then (2R)-(-)-glycidyl 3-nitrobenzenesulfonate was added and stirred overnight. The reaction was worked up by pouring into water and ether. The ether layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The yield of (R)-2,3-dichlorophenyl glycidyl ether was 0.837 g.

Using the method of Example 6, *supra*, (R)-2,3-dichlorophenyl glycidyl ether (0.837 g, 3.82 mmol) and

1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (0.75 g, 4.18 mmol) were used to prepare 860 mg of the title compound as a white solid: GC/EI-MS,  $m/z$ , (rel. int.) 382 (M-15, .1), 280 (11), 278 (64), 277 (16), 276 (100), 163 (10), 121 (35), 77 (10), 71 (24), 70 (27), 58 (12).

EXAMPLE 67: Preparation of (S)-N-[2-Hydroxy-3-(2,3-dichlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride. Compound 116

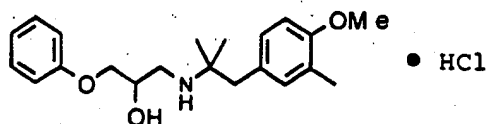


2,3-Dichlorophenol (0.69 g, 4.24 mmol) was dissolved in 15 mL of acetone, followed by the addition of powdered potassium carbonate (1.6 g, 11.57 mmol). This mixture was stirred for 2 hours then (2S)-(+)-glycidyl 3-nitrobenzenesulfonate was added and stirred overnight. The reaction was worked up by pouring into water and ether. The ether layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The yield of (S)-2,3-dichlorophenyl glycidyl ether was 0.84 g.

Using the method of Example 6, *supra*, (S)-2,3-dichlorophenyl glycidyl ether (0.84 g, 3.82 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (0.75 g, 4.18 mmol) were used to prepare 860 mg of the title compound as a white solid: GC/EI-MS,  $m/z$ , (rel. int.) 382 (M-15, .1), 280 (10), 279 (9), 278 (63), 276 (100), 163 (11), 121 (28), 77 (7), 71 (21), 70 (23), 58 (10).

EXAMPLE 68: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-methoxy-3-methylphenyl)ethylamine Hydrochloride. Compound 117

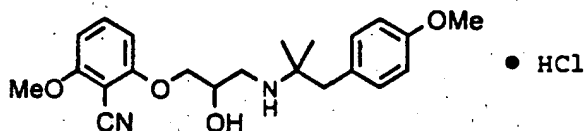
84



Using the method of Example 64, *supra*, 4-hydroxy-3-methylbenzyl alcohol (1.0 g, 7.25 mmol), 2-nitropropane (5 mL), and tetrabutylammonium fluoride (0.38 g, 0.145 mmol) were used to prepare 0.8 g of 1,1-dimethyl-2-(4-methoxy-3-methylphenyl)ethylamine.

Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (0.151 g, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxy-3-methylphenyl)ethylamine (0.2 g, 1.0 mmol) were used to prepare 130 mg of the title compound as a white solid: GC/EI-MS, *m/z*, (rel. int.) 328 (M-15, .1), 209 (14), 208 (100), 177 (5), 135 (14), 114 (5), 91 (6), 76 (9), 71 (8), 70 (13), 58 (5).

EXAMPLE 69: Preparation of N-[2-Hydroxy-3-(2-cyano-3-methoxyphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine Hydrochloride, Compound 118



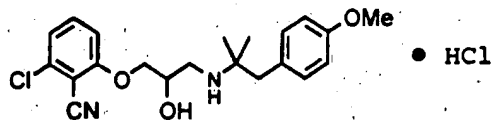
Powdered sodium cyanide (9.0 g, 184 mmol) and 2,6-dimethoxybenzonitrile were added to 50 mL of dimethylsulfoxide and heated to 145 °C for 110 min under nitrogen. The reaction was cooled and poured into ether and dilute HCl. The ether layer was separated, washed twice with dilute acid, once with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The yield of 2-cyano-3-methoxyphenol was 8.1 g.

2-Cyano-3-methoxyphenol (1 g, 6.7 mmol) and powdered potassium carbonate (2.78 g, 20.1 mmol) were stirred in 15 mL of acetone for 5 minutes, followed by addition of epibromohydrin (1.38 g, 10.1 mmol). The mixture was stirred for 72 hours then poured into water/ether. The ether layer was separated, washed with sodium carbonate and saturated brine, dried over anhydrous sodium sulfate, and concentrated. The resulting crude solid was triturated with ether/hexane, filtered, and dried under vacuum to give 0.44 g of 2-cyano-3-methoxyphenyl glycidyl ether.

Using the method of Example 6, *supra*, 2-cyano-3-methoxyphenyl glycidyl ether (0.205 g, 1.0 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (0.215 g, 1.2 mmol) were used to prepare 265 mg of the title compound as a white solid:  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  9.6 (1H, br s), 8.2 (1H, br s), 7.4 (1H, t), 7.15 (2H, d), 6.8 (2H, d), 6.6 (1H, d), 6.53 (1H, d), 4.75 (1H, m), 4.25 (2H, m), 3.87 (3H, s), 3.77 (3H, s), 3.43 (2H, m), 3.12 (2H, dd), 1.45 (3H, s), 1.41 (3H, s).  $^{13}\text{C-NMR}$   $\delta$  162.9, 162, 159.3, 135.5, 132.4, 127, 114.7, 114.4, 105.6, 104.6, 92.2, 71.4, 66.1, 61.9, 56.8, 55.8, 45.4, 43.8, 23.5, 23.3.

EXAMPLE 70: Preparation of N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine Hydrochloride. Compound 119

25

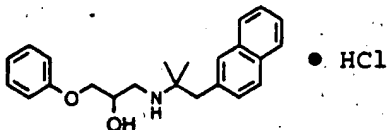


Using the method of Example 69, *supra*, 3-chloro-2-cyanophenol (made using the method of Example 60, *supra*) (0.48 g, 3.13 mmol), potassium carbonate (1.3 g, 9.38 mmol),

and epibromohydrin (0.86 g, 6.25 mmol) were used to prepare 93 mg of 3-chloro-2-cyanophenyl glycidyl ether.

Using the method of Example 6, *supra*, 3-chloro-2-cyanophenyl glycidyl ether (0.093 g, 0.44 mmol) and  
5 1,1-dimethyl-(4-methoxyphenyl)ethylamine (0.095 g, 0.53 mmol) were used to prepare 134 mg of the title compound as a white solid: <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 9.68 (1H, br s), 8.2 (1H, br s), 7.4 (1H, t), 7.15 (2H, d), 7.03 (1H, d), 6.95 (1H, d), 6.8 (2H, d), 5.7 (1H, br s), 4.8 (1H, m), 4.3 (2H, d), 3.75 (3H, s),  
10 3.4 (2H, m), 3.13 (2H, dd), 1.44 (3H, s), 1.40 (3H, s).

EXAMPLE 71: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(2-naphthyl)ethylamine Hydrochloride, Compound 120



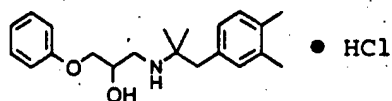
15 Using the method of Example 52, *supra*, 2-amino-methylnaphthalene (2.51 g, 16 mmol) was used to prepare 1.9 g of 1,1-dimethyl-2-(2-naphthyl)ethylamine.

Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (0.163 g, 1.1 mmol) and 1,1-dimethyl-2-(2-naphthyl)ethylamine (0.26 g, 1.3 mmol) were used to  
20 prepare 243 mg of the title compound as a white solid: GC/EI-MS, *m/z*, (rel. int.) 334 (M-15, .1), 209 (14), 208 (100), 141 (16), 115 (7), 76 (5), 70 (7).

EXAMPLE 72: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(3,4-dimethylphenyl)ethylamine Hydrochloride, Compound 121



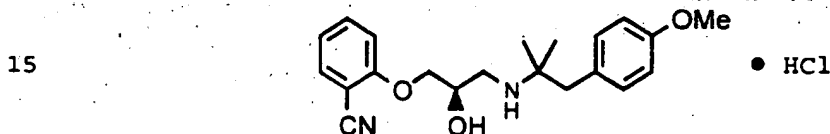
87



Using the method of Example 52, *supra*, 3,4-dimethylbenzylamine (5 g, 37 mmol) was used to prepare 2.29 g of 1,1-dimethyl-2-(3,4-dimethylphenyl)ethylamine.

5 Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (0.165 g, 1.1 mmol) and 1,1-dimethyl-2-(3,4-dimethylphenyl)ethylamine (0.22 g, 1.2 mmol) were used to prepare 268 mg of the title compound as a white solid: GC/EI-MS, *m/z*, (rel. int.) 312 (M-15,1), 209 (14), 208 (100),  
 10 133 (5), 119 (13), 114 (5), 107 (5), 91 (5), 76 (10), 71 (8), 70 (14), 58 (6).

EXAMPLE 73: Preparation of (R)-N-[2-Hydroxy-3-(2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 122



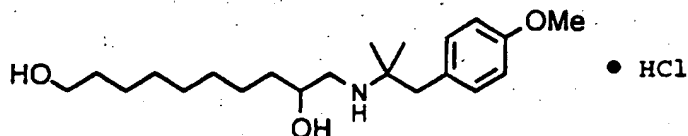
15 Using the method of Example 60, *supra*, 2-cyanophenol (0.54 g, 4.5 mmol), sodium hydride (0.188 g, 4.7 mmol), and (2R)-(-)-glycidyl 3-nitrobenzenesulfonate (1.06 g, 4.1 mmol) were used to prepare 350 mg of (R)-2-cyanophenyl glycidyl  
 20 ether.

Using the method of Example 6, *supra*, (R)-2-cyanophenyl glycidyl ether (0.35 g, 2.0 mmol) and 1,1-dimethyl-(4-methoxyphenyl)ethylamine (0.35 g, 1.96 mmol) were used to prepare 600 mg of the title compound as a white solid: <sup>1</sup>H-NMR  
 25 (CDCl<sub>3</sub>) δ 9.7 (1H, br s), 8.2 (1H, br s), 7.5 (2H, m), 7.15 (2H, d), 7.0 (2H, m), 6.8 (2H, d), 4.8 (1H, br m), 4.25 (2H,

m), 3.75 (3H, s), 3.45 (2H, m), 3.12 (2H, dd), 1.45 (3H, s), 1.41 (3H, s).

EXAMPLE 74: Preparation of N-(2,10-Dihydroxydecyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride.

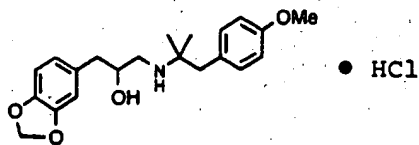
5 Compound 123



Using the method of Example 9, *supra*, 1,2-epoxy-10-hydroxydecane (172 mg, 1 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (230 mg, 1.5 mmol) were used to  
10 prepare the hydrochloride salt of the title compound. MPLC of the free amine (silica gel, 1% MeOH/CHCl<sub>3</sub>), followed by treatment with an excess of 1 M HCl/ether, yielded 130 mg of the title compound as a white powder: GC/EI-MS, *m/z* (rel. int.) 336 (*M*<sup>+</sup> - 15, 1), 231 (14), 230 (100), 212 (9), 163  
15 (10), 122 (5), 121 (42), 91 (8), 78 (6), 77 (5), 71 (13), 70 (11), 58 (8), 55 (8), 41 (6).

EXAMPLE 75: Preparation of N-[2-hydroxy-3-(3,4-methylene-dioxyphenyl)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine Hydrochloride. Compound 124

20

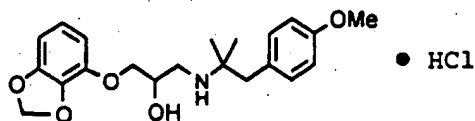


Safrole oxide was prepared by stirring a solution of safrole (1.48 mL, 10 mmol) and *m*-chloroperoxybenzoic acid (2.70 g, 11 mmol) in methylene dichloride (25 mL) overnight. The reaction was quenched by pouring into water (50 mL). The

aqueous was extracted with ether (3 x 25 mL). The organic layers were combined and washed with 10% aqueous sodium sulfate (2 x 25 mL), saturated aqueous sodium bicarbonate (3 x 25 mL), and brine (25 mL). The organic phase was dried over magnesium sulfate and the solvents were removed in vacuo. The resulting yellow oil was used without further purification.

To a solution of safrole oxide (196 mg, 1.1 mmol) in acetonitrile (1.0 mL) was added lithium perchlorate (107 mg). The solution was stirred at ambient temperature to dissolve all of the solid lithium perchlorate. To this solution was added 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (180 mg, 1.0 mmol) and the reaction was stirred at 50 °C overnight. To the cooled reaction mixture was added water (5 mL) and was subsequently extracted with methylene dichloride (3 x 1 mL). The combined organic phases were washed with water (1 mL) and brine (1 mL) and dried over magnesium sulfate. The crude orange oil was purified (MPLC, silica gel, 1% MeOH/CHCl<sub>3</sub>) and dissolved in methylene dichloride (5 mL). The hydrochloride salt was prepared by adding an excess of 1 M HCl/ether. The solvents were removed in vacuo to yield 139 mg of thick oil: GC/EI-MS, *m/z* (rel. int.) 342 (M<sup>+</sup>, .1), 237 (15), 236 (100), 163 (5), 136 (6), 135 (61), 121 (23), 78 (7), 77 (13), 70 (15), 58 (7).

25 EXAMPLE 76: Preparation of N-[2-hydroxy-3-(3,4-methylene-dioxyphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine Hydrochloride. Compound 125

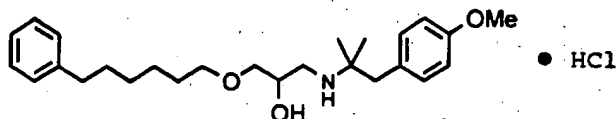


Using the method of Example 9, *supra*, 1,2-epoxy-3-(3,4-methylenedioxyphenoxy)propane (194 mg, 1 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (180 mg, 1 mmol) were used to prepare the hydrochloride salt of the title compound.

5 MPLC of the free amine (silica gel, 1% MeOH/CHCl<sub>3</sub>), followed by treatment with an excess of 1 M HCl/ether, yielded 88 mg of a white powder: GC/EI-MS, *m/z* (rel. int.) 374 (M<sup>+</sup>, .0), 253 (15), 252 (100), 137 (8), 121 (16), 114 (8), 71 (12), 70 (8).

EXAMPLE 77: Preparation of N-[2-hydroxy-3-(6-phenyl-hexanoxyl)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

10 Compound 126



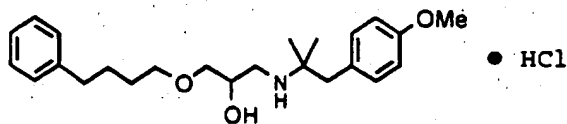
Using the method of Example 9, *supra*, 6-phenyl-hexylglycidyl ether (337 mg, 1.44 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (180 mg, 1 mmol) were used to prepare the title compound. Preparative TLC (20 cm x 20 cm x 2 mm silica, eluted with 1% MeOH/CHCl<sub>3</sub>) was used to purify the material and yielded 275 mg of free base: GC/EI-MS, *m/z* (rel. int.) 398 (M<sup>+</sup> - 15, .1), 293 (21), 292 (100), 163 (10), 121 (19), 114 (9), 91 (5), 90 (45), 71 (13), 70 (14), 58 (9).

15

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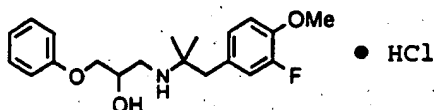
EXAMPLE 78: Preparation of N-[2-hydroxy-3-(4-phenyl-butanoxyl)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 127



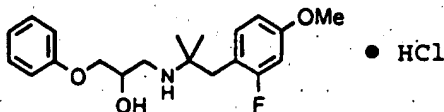
Using the method of Example 9, *supra*, 4-phenylbutyl glycidyl ether (348 mg, 1.5 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (268 mg, 1.5 mmol) were used to prepare the title compound. Preparative TLC (20 cm x 20 cm x 5 2 mm silica, eluted with 5%MeOH/CHCl<sub>3</sub>) was used to purify the material and yielded 275 mg of free base: GC/EI-MS, *m/z* (rel. int.) 370 (*M*<sup>+</sup> - 15, .1), 265 (19), 264 (100), 163 (11), 121 (19), 114 (9), 90 (43), 71 (10), 70 (12), 58 (7).

EXAMPLE 79: Preparation of N-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(3-fluoro-4-methoxyphenyl)ethylamine, Compound 128



Using the method of Example 6, *supra*, phenyl glycidyl ether (150 mg, 1.1 mmol) and 1,1-dimethyl-2-(3-fluoro-4-methoxyphenyl)ethylamine (197 mg, 1 mmol) were used to prepare the title compound. The title compound crystallized on standing to yield 169 mg of small crystals: GC/EI-MS, *m/z* (rel. int.) 332 (*M*<sup>+</sup> - 15, .1), 209 (16), 208 (100), 139 (13), 133 (5), 114 (7), 107 (6), 77 (11), 71 (12), 70 (20), 58 (9):

EXAMPLE 80: Preparation of N-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(2-fluoro-4-methoxyphenyl)ethylamine Hydrochloride, Compound 129

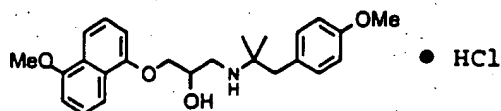


Using the method of Example 6, *supra*, phenyl glycidyl ether (150 mg, 1.1 mmol) and 1,1-dimethyl-2-(2-fluoro-

4-methoxyphenyl)ethylamine (197 mg, 1 mmol) were used to prepare the title compound. Preparative HPLC ( $C_{18}$ , reversed-phase, eluted with 1% HCl/ $CH_3CN$  gradient) was used to purify the compound, yielding 301 mg of a white powder:

- 5 GC/EI-MS,  $m/z$  (rel. int.) 332 ( $M^+$  - 15, 1), 209 (15), 208 (100), 139 (14), 114 (5), 107 (5), 77 (6), 71 (7), 70 (13), 58 (5).

EXAMPLE 81: Preparation of N-(2-hydroxy-3-(5-methoxy-1-naphthoxy)propyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
10 Hydrochloride, Compound 130



- Potassium carbonate (13 mmol) was added to a solution of 1,5-dihydroxy naphthalene (6.2 mmol) in acetone in a sealed vacuum tube. The tube was heated to 70 °C for 30 minutes.  
15 Iodomethane (9.4 mmol) was added and the tube heated to 70 °C overnight.

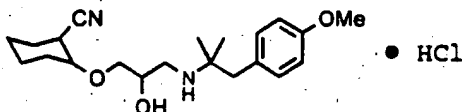
- The reaction mixture was partitioned between ether and 10% aqueous HCl. The ether layer was separated and extracted with 0.5 M KOH. The water layer was separated and acidified  
20 with 10% aqueous HCl and extracted into ether. The ether layer was separated and dried over magnesium sulfate and evaporated to a solid. The solid was purified using reverse phase HPLC using a acetonitrile/0.1% HCl gradient yielding 179 mg 1-hydroxy-5-methoxy naphthalene.

- 25 Sodium hydride (60% suspension in mineral oil, 1 mmol) was added to a solution of 1-hydroxy-5-methoxy naphthalene (1 mmol) and stirred 10 minutes. Epichlorohydrin (1 mmol) was added and the reaction stirred at 70 °C for 72 hours. The reaction mixture was diluted with 1 liter of saturated sodium

chloride solution and extracted into ether. The ether layer was then washed with water, separated and dried over anhydrous sodium sulfate and evaporated to give 5-methoxy-napthalene glycidyl ether.

- 5        Using the method of Example 6, *supra*, 5-methoxy-napthalene glycidyl ether (1 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1 mmol) yielded 161 mg of the title compound as a white solid: GC /EI-MS, m/z (rel. int.) 360 (M<sup>+</sup>, 1), 289 (18), 288 (100), 173 (8), 121 (20), 71 (18),  
10   70 (12).

EXAMPLE 82: Preparation of N-[2-hydroxy-3-(2-cyano-cyclohexyloxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethyl-amine Hydrochloride. Compound 131

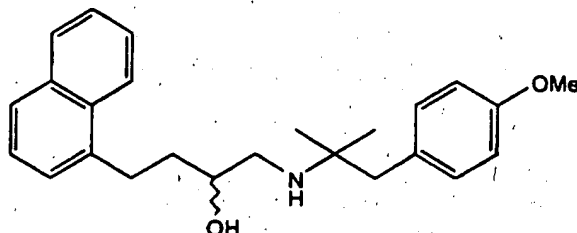


- 15        Sodium hydride (60% suspension in mineral oil, 60 mg, 1.59 mmol) was added to a solution of trans-2-cyano-cyclohexanol in N,N-dimethylformamide (2.0 mL) and stirred for 10 minutes at room temperature. Epibromohydrin (0.22 g, 1.59 mmol) was then added and the reaction stirred for an  
20   additional 3 hours. The solution was partitioned between diethyl ether/water, and the layers separated. The ether layer was washed with water (3 X 100 mL) and dried over magnesium sulfate and evaporated to give 0.17 g of 2-cyanocyclohexyl glycidyl ether.
- 25        Using the method of Example 6, *supra*, 2-cyanocyclohexyl glycidyl ether (0.94 mmol) and 1,1-dimethyl-2-(4-methoxy-phenyl)ethylamine (1.17 mmol) yielded 55 mg of the title compound as a white solid: GC /EI-MS, m/z (rel. int.) 360

(M+, 1), 239 (100), 121 (22), 240 (14), 70 (11), 163 (8), 71 (8), 81 (7).

EXAMPLE 83: Synthesis of (R/S)-1-[[2,2-dimethyl-(4-methoxy) phenethyl]amino-2-hydroxy-4(1'-naphthyl)-butane.

5 Compound 162



A solution of 1-chloromethylnaphthalene (750  $\mu$ L, 5 mmol, Aldrich) in anhydrous ether (10 mL) was added dropwise to 25 mL of allyl magnesium bromide (1 M in ether) over 30 minutes.

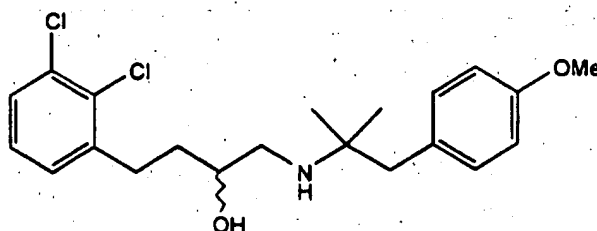
- 10 The resulting mixture was heated at reflux for 14 hours. After cooling the reaction to room temperature, it was quenched with 25 mL of saturated  $\text{NH}_4\text{Cl}$  (aqueous). The layers were separated and the organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to give 1 g of 1-but-3-enyl-naphthalene that was carried without further purification.

- 15 1-But-3-enyl-naphthalene (1 g) from above was added to a solution of 50% mCPBA (2.1 g) in  $\text{CH}_2\text{Cl}_2$  (50 mL) and the reaction stirred at room temperature for 48 hours. The material was diluted with  $\text{CH}_2\text{Cl}_2$ , and was extracted with sodium sulfite (aqueous) and  $\text{NaHCO}_3$  (aqueous), dried over  $\text{MgSO}_4$ , filtered and evaporated to give 1-[(2-oxoaryl)ethyl]-naphthalene (1 g) that was carried without further purification.



A solution of 1-[(2-oxoaryl)ethyl]-naphthalene (1 g) and 1,1-dimethyl-2-(4-methoxyphenyl) ethylamine (985 mg, 5.5 mmol) in ethanol (25 mL) was heated at reflux for 12 hours. The reaction was evaporated and the residue dissolved in 4 N HCl/dioxane. Upon addition of ether, crystals formed and were subsequently collected and dried in a vacuum oven to give 1.4 g of (R/S)-1-[[2,2-dimethyl-(4'methoxy)-phenethyl]]amino-2-hydroxy-4(1'-naphthyl)-butane. ESMS [(M+H)<sup>+</sup> = 378, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 360MHz) @300°K δ 8.06 (1H, d of d), 7.83 (1H, d of d), 7.78-7.61 (2H, m), 7.49-7.35 (3H, m), 7.09-7.02 (2H, m), 6.84-6.79 (2H, m), 3.76 (3H, s), 3.61 (1H, m), 3.33-3.09 (2H, m), 2.77-2.72 (1H, d of d), 2.62 (2H, s), 2.47-2.42 (1H, m), 1.85-1.82 (2H, m), 1.04 (6H, s).

Example 84 Synthesis of (R/S)-1-[[2,2-dimethyl-(4'methoxy)phenethyl]]amino-2-hydroxy-4(1'-2,3-dichlorophenyl)]-butane. Compound 163.

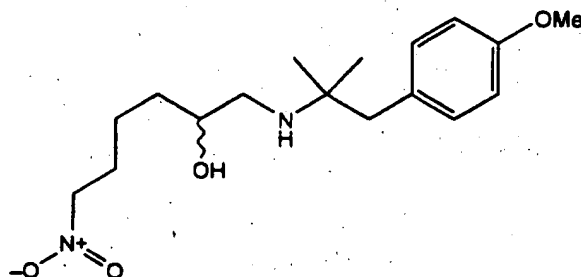


Starting from 2,3-dichlorobenzylchloride (1g, 5 mmol) and following the three step procedure described in Example 83, 660 mg of (R/S)-1-[[2,2-dimethyl-(4'methoxy)-phenethyl]]amino-2-hydroxy-4(1'-(2,3-dichlorophenyl)]-butane was synthesized and isolated as white crystals. ESMS [(M+H)<sup>+</sup> = 396 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 360 MHz) @ 300°K δ 7.3 (1H, d of d), 7.18 (1H, d of d), 7.10-7.03 (3H, m), 6.82-6.80 (2H, m), 3.78

(3H, s), 3.47 (1H, m), 2.97-2.83 (2H, m), 2.74 (1H, m) 2.60 (2H, s), 2.43-2.37 (1H, m), 1.71 (2H, m), 1.04 (6H, s).

Example 85: Synthesis of (R/S)-1-nitro-5-hydroxy-6-[1,1-dimethyl-2-(4-methoxyphenyl)]hexane, Compound 164

5



Starting from 6-nitro-1-hexene (1 g, 7.75 mmol) and following the two last steps described in Example 83, 1 g of (R/S)-1-nitro-5-hydroxy-6-[1,1-dimethyl-2-(4-methoxyphenyl)]hexane was synthesized and isolated as tan crystals. ESMS [M+H]<sup>+</sup>=325 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 360 MHz) @ 300°K δ 7.00 (4H, d of d), 4.37 (2H, t), 3.77 (3H, s), 3.49 (1H, m), 2.74 (1H, d of d), 2.61 (2H, s), 2.35 (1H, m) 2.03 (2H, m), 1.60-1.43 (4H, m) 1.08 (6H, s).

EXAMPLE 86: Additional compounds

Additional compounds were synthesized using techniques along lines as those described above. Examples of such compounds include the following:

Compound 1: N-[2-hydroxy-3-(2-hydroxybenzimidazol-4-oxyl)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 14: (R)-N-[2-hydroxy-3-(1-naphthoxy)propyl]-1-methyl-3-methoxybenzylamine.

Compound 22: N-(3-phenylpropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 24: *N*-(4-phenylbutyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 34: *N*-(Benzyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

5       Compound 36: *N*-(4-phenoxybutyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 42: *N*-(3-(1-naphthoxy)propyl)-1,1-dimethyl-2-(4-methoxyphenyl).

10       Compound 52: *N*-[2-hydroxy-3-(2-acetamidophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 53: *N*-(2-phenoxyethyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 54: *N*-2-hydroxy-3-(4-tert-butylphenoxy)propyl]-1,1-dimethyl-2-phenylethylamine.

15       Compound 55: *N*-[2-hydroxy-3-(1-naphthoxy)propyl]-1,1-dimethyl-2-phenylethylamine.

Compound 58: *N*-[2-hydroxy-3-(4-acetamidophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

20       Compound 60: *N*-[2-hydroxy-3-(2-phenylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 61: *N*-[2-hydroxy-3-(3-phenylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 62: *N*-[2-Hydroxy-3-(4-phenylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

25       Compound 84: *N*-(2-Phenylethyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 92: *N*-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(1-naphthyl)ethylamine.

30       Compound 93: *N*-(2-hydroxy-3-cyclohexoxypropyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine.

Compound 102: *N*-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(4-ethoxyphenyl)ethylamine.

Compound 132: N-[2-hydroxy-3-(3,4-dimethoxy-  
phenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
Hydrochloride; GC/EI-MS, m/z (rel. int.) 390 (M+, .0), 269  
(17), 268 (100), 163 (6), 153 (5), 121 (21), 114 (17), 77  
5 (5), 71 (19), 70 (17), 58 (7).

Compound 133: N-[2-hydroxy-3-(3,5-dimethoxy-  
phenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
Hydrochloride; GC/EI-MS, m/z (rel. int.) 390 (M+, .0), 269  
(16), 268 (100), 193 (9), 163 (8), 154 (7), 121 (24), 114  
10 (46), 76 (6), 71 (11), 70 (18).

Compound 134: N-[2-hydroxy-3-(2-carbomethoxy-  
phenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
Hydrochloride; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.42 (s, 3H), 1.44 (s, 3H),  
3.2 (dd, 2H), 3.3-3.6 (bm, 2H), 3.7 (s, 3H), 3.8 (s, 3H),  
15 4.1-4.4 (m, 3H), 4.7 (m, 1H), 6.8 (d, 2H), 7.0 (m, 2H), 7.2  
(d, 2H), 7.5 (t, 1H), 7.8 (d, 1H), 8.8 (m, 1H), 9.3 (m, 1H).

Compound 135: N-[2-hydroxy-3-(4-methylphenoxy)propyl]-  
1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride;  
GC/EI-MS, m/z (rel. int.) 328 (M-15, .1), 223 (15), 222 (100),  
20 163 (6), 147 (6), 121 (23), 114 (9).

Compound 136: N-[2-hydroxy-3-(2,3-dichlorophenoxy)-  
propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
Hydrochloride; GC/EI-MS, m/z (rel. int.) 382 (M-15, .1), 280  
(10), 279 (9), 278 (62), 276 (100), 163 (11), 121 (28).

Compound 137: N-[2-hydroxy-3-(3,5-dichlorophenoxy)-  
propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
Hydrochloride; GC/EI-MS, m/z (rel. int.) 382 (M-15, .1), 280  
(11), 279 (9), 278 (65), 277 (16), 276 (100), 163 (8), 146  
(5), 144 (5).

Compound 138: N-[2-hydroxy-3-(2,4-dichloro-  
phenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
Hydrochloride; GC/EI-MS, m/z (rel. int.) 382 (M-15, .1), 280

(11), 279 (9), 278 (65), 277 (5), 276 (100), 163 (10), 161 (6), 132 (5).

Compound 139: N-[2-hydroxy-3-(3,4-dichlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
5 Hydrochloride; GC/EI-MS, m/z (rel. int.) 382 (M-15,.1), 279 (10), 279 (9), 278 (63), 276 (100), 163 (9), 146 (5), 121 (29).

Compound 140: N-[2-hydroxy-3-(2,5-dichlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
10 Hydrochloride; GC/EI-MS, m/z (rel. int.) 382 (M-15,.1), 280 (11), 279 (9), 278 (64), 276 (100), 163 (9), 161 (5), 121 (29), 113 (8).

Compound 141: N-[2-hydroxy-3-(4-ethylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride;  
15 GC/EI-MS, m/z (rel. int.) 342 (M-15,.1), 237 (15), 236 (100), 163 (5), 121 (19), 114 (7).

Compound 142: N-[2-hydroxy-3-(2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride;  
GC/EI-MS, m/z (rel. int.) 339 (M-15,1), 234 (15), 233 (100),  
20 163 (5), 121 (14).

Compound 143: N-[2-hydroxy-3-(3-nitrophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride;  
GC/EI-MS, m/z (rel. int.) 359 (M-15,.1), 254 (15), 253 (100),  
163 (5), 121 (15).

Compound 144: N-[2-hydroxy-3-(4-ethoxyphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride;  
GC/EI-MS, m/z (rel. int.) 358 (M-15,.1), 253 (17), 252 (100),  
163 (6), 121 (21), 114 (8), 108 (8).

Compound 145: N-[2-hydroxy-3-(4-iso-propylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine  
30 Hydrochloride; GC/EI-MS, m/z (rel. int.) 356 (M-15,.1), 251 (18), 250 (100), 163 (7), 121 (23), 117 (7), 114 (8).

Compound 146: N-[2-hydroxy-3-(3-iso-propyl-phenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 356 (M-15,.1), 251 (18), 250 (100), 163 (6), 121 (21), 117 (5), 114 (10), 91 (9).

Compound 147: N-[2-hydroxy-3-(3-ethoxyphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 358 (M-15,1), 253(16), 252 (100), 163 (5), 121 (20), 114 (12), 77 (5).

Compound 148: N-[2-hydroxy-3-(2-n-propylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 356 (M-15,1), 251(17), 250 (100), 163 (6), 121 (34), 114 (9), 107 (6), 90 (17), 78 (9), 77 (10), 71 (17).

Compound 149: N-[2-hydroxy-3-(4-n-propylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 356 (M-15,.8), 251(18), 250 (100), 163 (5), 121 (19), 114 (7), 110 (5), 107 (7), 91 (6).

Compound 150: N-[2-Hydroxy-3-(3-ethylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 342 (M-15,.6), 237(16), 236 (100), 163 (5), 121 (21), 114 (6), 105 (5), 90 (6).

Compound 151: N-[2-hydroxy-3-(2-ethylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 342 (M-15,1), 237 (16), 236 (100), 163 (5), 121 (17), 114 (7), 91 (6), 77 (7).

Compound 152: N-[2-hydroxy-3-(4-trifluoromethoxyphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 398 (M-15,2), 293(15), 292 (100), 121 (20), 77 (5).

Compound 153: N-[2-hydroxy-3-(2-iso-propyl-phenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 356 (M-15,1), 251

(19), 250 (100), 163 (5), 122 (5), 121 (53), 114 (8), 104 (6), 103 (6), 91 (24), 77 (14).

Compound 154: N-[2-hydroxy-3-(3-trifluoromethoxyphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 398 (M-15,.1), 293 (15), 292 (100), 163 (7), 121 (18).

Compound 155: N-[2-hydroxy-3-(2,6-dichlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 382 (M-15,.1), 279 (11), 279 (9), 277 (64), 275 (100), 163 (11), 163 (5), 161 (6), 121 (33), 114 (12).

Compound 156: N-[2-hydroxy-3-(3,5-bistrifluoromethylphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 450 (M-15,.1), 345 (16), 344 (100), 213 (5), 163 (8), 121 (20).

Compound 157: N-[2-hydroxy-3-(3-chloro-5-methoxyphenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 378 (M-15,.1), 275 (5), 274 (34), 273 (16), 272 (100), 163 (5), 121 (17), 114 (8).

Compound 158: N-[2-hydroxy-3-(4-nitrophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 359 (M-15,.1), 254 (14), 253 (100), 121 (12).

Compound 159: N-[2-hydroxy-3-(2-nitrophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 359 (M-15,.1), 254 (15), 253 (100), 163 (6), 121 (17), 114 (10), 96 (5), 78 (5).

Compound 160: N-[2-hydroxy-3-(3-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 339 (M-15,.1), 234 (15), 233 (100), 121 (21), 102 (7), 90 (6).

Compound 161: N-[2-hydroxy-3-(4-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride; GC/EI-MS, m/z (rel. int.) 339 (M-15,1), 234 (16), 233 (100), 163 (5), 121 (15), 102 (5).

5 Compound 166: N-[2R-Hydroxy-3-[(2-cyanobenzthien-3-yloxy)propyl]-1,1-dimethyl-2-(3,4-dichlorophenyl)ethylamine. Prepared as a hydrochloride salt, MS (ES) m/e 449 [M+H]<sup>+</sup>.

Compound 167: R-1-[1,1 Dimethyl-2-(4-methoxyphenyl)ethylaminol-3-(2'-carbazoloxyl)pran-2-ol. Prepared as a  
10 trifluoroacetate salt, MS (ES) m/e 419.2 [M+H]<sup>+</sup>.

Compound 168: N-[2R-Hydroxy-3-[(2-bromopyridinyloxy)-propyl]-1,1-dimethyl-2-(4-methoxy)ethylamine. Prepared as a hydrochloride salt, MS (ES) m/e 411,409 [M+H]<sup>+</sup>.

Compound 169: N-(2-hydroxy-3-(3-N,N-dimethylphenoxy)propyl)-1,1-dimethyl-2-(-4-methoxyphenyl)ethylamine, GC/MS  
15 251(100), 176(9), 163(5), 138(11), 137(6), (8), 125(10), 121(23), 114(46), 108(6), 77(6), 76(7), (10), 70(14), 42(8).

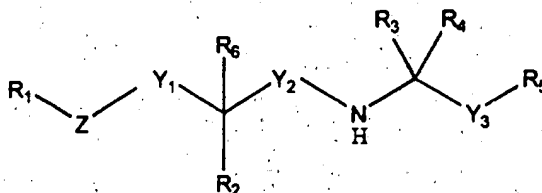
Compound 170: N-(2-hydroxy-3-(3-phenylphenoxy)propyl)-1,1-dimethyl-2-(-4-methoxyphenyl)ethylamine. GC/MS (mt,  
20 0.1), 284(100), 121(28), 285 (27), 152(13), 70(13), 71(11), 153(10).

Other embodiments are within the following claims. Thus, while several embodiments have been shown and described, various modifications may be made, without  
25 departing from the spirit and scope of the present invention.



CLAIMS

1. A compound having the chemical formula:



wherein  $R_1$  is selected from the group consisting of:

- 5 aryl, longer-length alk, and cycloalk;

$R_2$  is selected from the group consisting of: lower alk, cycloalk, alkoxy, H, OH, =O, C(O)OH, C(O)O-lower alk, C(O)NH-lower alk, C(O)N(lower alk)<sub>2</sub>, SH, S-lower alk, NH<sub>2</sub>, NH-lower alk, and N(lower alk)<sub>2</sub>;

- 10  $R_3$  and  $R_4$  is each independently lower alk or together cyclopropyl;

- $R_5$  is either an optionally substituted naphthyl having one to four substituents independently selected from the group consisting of methyl, ethyl, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, or a substituted phenyl having one to four substituents with at least one substituent in a meta or para position selected from the group consisting of: lower alkyl, methoxy, Cl, F, Br, and lower haloalkoxy, provided that said substituted phenyl may also have 2 to 3 additional substituents;
- 15 20

$R_6$  if present is either hydrogen, lower alkyl or lower alkenyl, wherein  $R_6$  is not present if  $R_2$  is =O;

$Y_1$  is either covalent bond, alkylene, or alkenylene;

$Y_2$  is alkylene;

- 25  $Y_3$  is alkylene;

$Z$  is selected from the group consisting of: covalent bond, O, S, NH, N-lower alk, alkylene, alkenylene, and

alkynylene, provided that if Z is either O, S, NH, or N-lower alk, then Y<sub>1</sub> is not a covalent bond; further provided that Y<sub>1</sub> and Z may together be a covalent bond;

provided that R<sub>1</sub> is not 6-CN-2-pyridyl;

5 further provided that if R<sub>1</sub> is 3,4 dimethoxy-phenyl, then R<sub>1</sub> is not CH<sub>3</sub>(CH<sub>3</sub>)<sub>2</sub>O-phenyl; 2-cyclopentyl-phenyl; 2-Cl-phenyl; 2-CN-phenyl; 2-(3-furanyl)phenyl; or 4-(1,2,-benzisothiazol);

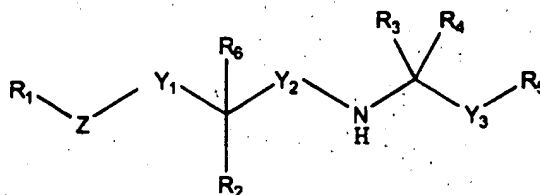
further provided that if R<sub>1</sub> is 4-methoxy-phenyl, then R<sub>1</sub> is not 2-cyclopentyl-phenyl; 2-CH<sub>3</sub>-phenyl; 2-benzyl-phenyl; 3-CH<sub>3</sub>, 4-CH<sub>3</sub>SO<sub>2</sub>-phenyl; 4-(1,2,-benzisothiazol);

further provided that if R<sub>1</sub> is 4-Cl-phenyl, then R<sub>1</sub> is not 2-CH<sub>3</sub>-phenyl, 5-iso-propyl-phenyl; 2-CH<sub>3</sub>-phenyl; 4-CH<sub>3</sub>-phenyl; phenyl; 2-Cl-phenyl; 4-Cl-phenyl; 2-methoxy, 4-CH<sub>3</sub>CHCH-phenyl; 3,4 CH<sub>3</sub>-phenyl; 2,4 CH<sub>3</sub>-phenyl; 2,3 CH<sub>3</sub>-phenyl; 2-iso-propyl, 5-CH<sub>3</sub>-phenyl; pridyl; 1-imidazole; or 4-(1,2,-benzisothiazol); and

further provided that if R<sub>1</sub> is 3,5 dimethyl, 4-methoxy-phenyl, then R<sub>1</sub> is not 4-CH<sub>3</sub>, 6-CN-2-pyridyl; or thiophenecarboxamide; and

20 pharmaceutically acceptable salts and complexes thereof; wherein said compound has an IC<sub>50</sub> ≤ 10 μM using the Calcium Receptor Inhibitor Assay.

2. A compound having the chemical formula:



25 wherein R<sub>1</sub> is either 2-CN-phenyl, 2,3-dichloro phenyl, 2-nitro-phenyl, 2-cyano-3-chloro-phenyl, an optionally

substituted pyridyl, an optionally substituted benzothiopyranyl, an optionally carbazole, or a longer-length alk;

$R_2$  is selected from the group consisting of: lower alk, cycloalk, alkoxy, H, OH, =O, C(O)OH, C(O)O-lower alk, C(O)NH-lower alk, C(O)N(lower alk), SH, S-lower alk, NH<sub>2</sub>, NH-lower alk, and N(lower alk);

$R_3$  and  $R_4$  is each independently lower alk or together cyclopropyl;

$R_5$  is either an optionally substituted naphthyl having one to four substituents independently selected from the group consisting of methyl, ethyl, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, or a substituted phenyl having one to four substituents with at least one substituent in a meta or para position selected from the group consisting of: lower alkyl, methoxy, Cl, F, Br, and lower haloalkoxy, provided that said substituted phenyl may also have 2 to 3 additional substituents;

$R_6$  if present is either hydrogen, lower alkyl or lower alkenyl, wherein  $R_6$  is not present if  $R_7$  is =O;

$Y_1$  is either covalent bond, alkylene, or alkenylene;

$Y_2$  is alkylene;

$Y_3$  is alkylene;

$Z$  is selected from the group consisting of: covalent bond, O, S, NH, N-lower alk, alkylene, alkenylene, and alkynylene, provided that if  $Z$  is either O, S, NH, or N-lower alk, then  $Y_1$  is not a covalent bond; further provided that  $Y_1$  and  $Z$  may together be a covalent bond; and

pharmaceutically acceptable salts and complexes thereof.

3. The compound of claim 2, wherein

$Y_1$  is methylene;

$Y_2$  is methylene; and

Y<sub>i</sub> is methylene.

4. The compound of claim 3, wherein R<sub>i</sub> is either 2-CN-phenyl, 2,3-dichloro phenyl, 2-nitro-phenyl, or 2-cyano-3-chloro-phenyl.

5. The compound of claim 3, wherein R<sub>i</sub> is either said optionally substituted pyridyl, said optionally substituted benzothiopyranyl, or said optionally carbazole wherein said optionally substituted pyridyl, said optionally substituted benzothiopyranyl, or said optionally carbazole is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, lower haloalkoxy, CF<sub>3</sub>, F, Cl, Br, CN, and NO<sub>2</sub>.

6. The compound of claim 3, wherein R<sub>i</sub> is either unsubstituted longer-length alkyl; unsubstituted longer-length alkenyl; monosubstituted longer-length alkyl with an optionally substituted cycloalkyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH; monosubstituted longer-length alkenyl with an optionally substituted cycloalkyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH; monosubstituted longer-length alkyl with an optionally substituted phenyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl,

halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH; monosubstituted longer-length alkenyl with an optionally substituted phenyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH; or an optionally substituted cycloalkyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH.

7. The compound of claim 6, wherein R<sub>1</sub> is either unsubstituted longer-length alkyl; unsubstituted longer-length alkenyl; or said optionally substituted cycloalkyl.

8. The compound of any of claims 2-7, wherein R<sub>2</sub> is OH or methoxy, R<sub>3</sub> is hydrogen, R<sub>4</sub> and R<sub>5</sub> is independently methyl or ethyl; and Z is O, S, or unsubstituted alkylene.

9. The compound of claim 8, wherein R<sub>1</sub> is OH, and Z is O.

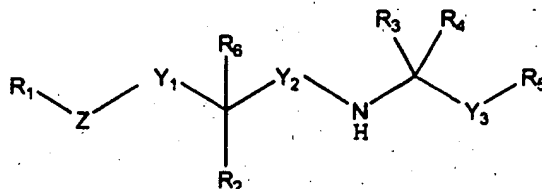
10. The compound of claim 8, wherein said compound is N-[2-hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine or a pharmaceutically acceptable salt or complex thereof

11. The compound of claims 2-7, wherein R<sub>2</sub> is hydrogen, R<sub>3</sub> is hydrogen,

$R_1$  and  $R_4$  is independently methyl or ethyl; and  
 $Z$  is O or methylene.

12. A pharmaceutical composition comprising a  
 pharmaceutically acceptable carrier and a therapeutically  
 5 effective amount of the compound of any of claims 1-11.

13. A method of treating a patient comprising the  
 step of administering to said patient a therapeutically  
 effective amount of a compound having the formula:



10 wherein  $R_1$  is selected from the group consisting of:  
 aryl, longer-length alk, and cycloalk;

$R_2$  is selected from the group consisting of: lower alk,  
 cycloalk, alkoxy, H, OH, =O, C(O)OH, C(O)O-lower alk, C(O)NH-  
 lower alk, C(O)N(lower alk), SH, S-lower alk, NH<sub>2</sub>, NH-lower

15 alk, and N(lower alk);

$R_3$  and  $R_4$  is each independently lower alk or together  
 cyclopropyl;

$R_5$  is aryl;

$R_6$  if present is either hydrogen, lower alkyl or lower  
 20 alkenyl, wherein  $R_6$  is not present if  $R_2$  is =O;

$Y_1$  is either covalent bond, alkylene, or alkenylene;

$Y_2$  is alkylene;

$Y_3$  is alkylene;

Z is selected from the group consisting of: covalent bond, O, S, NH, N-lower alk, alkylene, alkenylene, and alkynylene, provided that if Z is either O, S, NH, or N-lower alk, then Y<sub>1</sub> is not a covalent bond; further provided that Y<sub>1</sub> and Z may together be a covalent bond; and pharmaceutically acceptable salts and complexes thereof; wherein said patient has a disease or disorder characterized by one or more of the following: (1) an abnormal bone or mineral homeostasis; (2) an abnormal amount of an extracellular or intracellular messenger which is ameliorated by a compound able to effect one or more calcium receptor activities; or (3) an abnormal effect of an intracellular or extracellular messenger which is ameliorated by a compound able to affect one or more calcium receptor activities.

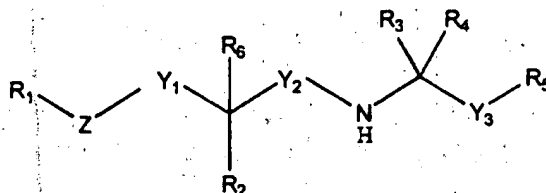
14. The method of claim 13, wherein said disease or disorder is characterized by said abnormal bone or mineral homeostasis.

15. The method of claim 14, wherein said bone or mineral disease or disorder is selected from the group consisting of: osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and osteoporosis.

16. The method of claim 15, wherein said bone or mineral disease or disorder is osteoporosis.

17. A method of treating a patient comprising the step of administering to said patient an amount of a compound sufficient to increase serum PTH level, said compound having the formula:

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wherein  $R_1$  is selected from the group consisting of:  
aryl, longer-length alk, and cycloalk;

$R_2$  is selected from the group consisting of: lower alk,  
5 cycloalk, alkoxy, H, OH, =O, C(O)OH, C(O)O-lower alk, C(O)NH-  
lower alk, C(O)N(lower alk), SH, S-lower alk, NH<sub>2</sub>, NH-lower  
alk, and N(lower alk);

$R_3$  and  $R_4$  is each independently lower alk or together  
cyclopropyl;

10  $R_5$  is aryl;

$R_6$  if present is either hydrogen, lower alkyl or lower  
alkenyl, wherein  $R_6$  is not present if  $R_2$  is =O;

$Y_1$  is either covalent bond, alkylene, or alkenylene;

$Y_2$  is alkylene;

15  $Y_3$  is alkylene

$Z$  is selected from the group consisting of: covalent  
bond, O, S, NH, N-lower alk, alkylene, alkenylene, and  
alkynylene, provided that if  $Z$  is either O, S, NH, or N-lower  
alk, then  $Y_1$  is not a covalent bond; further provided that  $Y_1$

20 and  $Z$  may together be a covalent bond; and

pharmaceutically acceptable salts and complexes thereof.

18. The method of claim 17, wherein said method is  
carried out by administering an amount of said compound  
effective to cause an increase in either duration, quantity,



or both duration and quantity, of serum PTH level sufficient to have a therapeutic effect.

19. The method of claims 17 or 18, wherein said compound is administered to said patient to cause an increase  
5 in serum PTH having a duration of one to twelve hours.

20. The method of claim 19, wherein said duration is about two to about four hours.

21. The method of claims 17 or 18, wherein said compound is administered to said patient to cause an increase  
10 in serum PTH up to 0.5 fold greater than peak serum PTH in said patient.

22. The method of claims 17 or 18, wherein said compound is administered to said patient to cause an increase  
15 in serum PTH 0.5 fold to 5 fold greater than peak serum PTH in said patient.

23. The method of claims 17 or 18, wherein said compound is administered to said patient to cause an increase  
in serum PTH 5 fold to 10 fold greater than peak serum PTH in said patient.

20 24. The method of claims 17 or 18, wherein said compound is administered to said patient to cause an increase  
in serum PTH at least 10 fold greater than peak serum PTH in said patient.

25 25. The method of any of claims 13-24, wherein R<sub>1</sub> is a substituted phenyl having one to four substituents each  
independently selected from the group consisting of: methoxy,

lower alkyl, OCF<sub>3</sub>, CFH<sub>2</sub>, CHF<sub>2</sub>, CF<sub>3</sub>, OCH<sub>2</sub>CF<sub>3</sub>, F, Cl, Br, I, OH, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, methylene dioxy, NH-lower alkyl, N(lower alkyl)<sub>2</sub>, C(O)lower alkyl, S-lower alkyl, S(O)lower alkyl, S(O)<sub>2</sub>lower alkyl, OC(O)lower alkyl, SC(O)lower alkyl, OC(S)lower alkyl, NHC(O)lower alkyl, N(lower alkyl)C(O)lower alkyl, NHC(S)lower alkyl, N(lower alkyl)C(S)lower alkyl, NHS(O)lower alkyl, N(lower alkyl)S(O)lower alkyl, C(O)OH, C(O)O-lower alkyl, C(O)NH<sub>2</sub>, C(O)NH-lower alkyl, C(O)N(lower alkyl)<sub>2</sub>, S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH-lower alkyl, and S(O)<sub>2</sub>N(lower alkyl)<sub>2</sub>.

26. The method of claim 25, wherein each R<sub>i</sub> substituent is independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH.

27. The method of claim 26, wherein R<sub>i</sub> is a substituted phenyl with at least one substituent in a meta or para position selected from the group consisting of: lower alkyl, methoxy, Cl, F, Br, and lower haloalkoxy, provided that said R<sub>i</sub> substituted phenyl may also have 2 to 3 additional substituents.

28. The method of any of claims 13-24, wherein R<sub>i</sub> is an optionally substituted naphthyl.

29. The method of claim 28, wherein R<sub>i</sub> is a substituted naphthyl having one to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH.

30. The method of claim 28, wherein R<sub>1</sub> is naphthyl.

31. The method of any of claims 13-30, wherein R<sub>1</sub> is either unsubstituted longer-length alkyl; unsubstituted longer-length alkenyl; monosubstituted longer-length alkyl  
5 with an optionally substituted cycloalkyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH; monosubstituted  
10 longer-length alkenyl with an optionally substituted cycloalkyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN,  
15 NO<sub>2</sub>, NH<sub>2</sub>, and OH; monosubstituted longer-length alkyl with an optionally substituted phenyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl,  
20 halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH; monosubstituted longer-length alkenyl with an optionally substituted phenyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN, NO<sub>2</sub>, NH<sub>2</sub>, and OH; or an optionally  
25 substituted cycloalkyl having up to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN,  
30 NO<sub>2</sub>, NH<sub>2</sub>, and OH.

32. The method of claim 31, wherein  $R_1$  is either unsubstituted longer-length alkyl, unsubstituted longer-length alkenyl, or said optionally substituted cycloalkyl.

33. The method of any of claims 13-30, wherein  $R_1$  is either an optionally substituted phenyl, an optionally substituted pyridyl, an optionally substituted benzothiopyranyl, an optionally carbazole.

34. The method of claim 33, wherein  $R_1$  is a substituted phenyl having one to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl, unsubstituted alkenyl, halogen, SH, CN,  $NO_2$ ,  $NH_2$ , and OH.

35. The method of claim 34, wherein  $R_1$  is either 2-CN-phenyl, 2,3-dichloro phenyl, 2-nitro-phenyl, or 2-cyano-3-chloro-phenyl.

36. The method of any of claims 13-35, wherein  $R_2$  is OH or alkoxy,  $R_3$  is hydrogen,  $R_1$  and  $R_4$  is each independently a lower alkyl; and Z is either O, S, or unsubstituted alkylene.

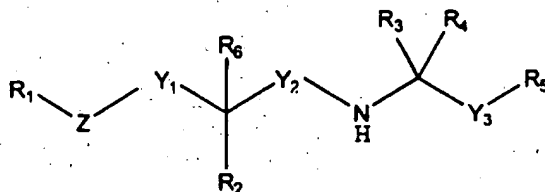
37. The method of claim 36, wherein  $R_2$  is OH or methoxy;  $Y_1$  is methylene;  $Y_2$  is methylene; and  $Y_3$  is methylene.

38. The method of claim 37, wherein  $R_1$  is methyl or ethyl; and  $R_4$  is methyl or ethyl.

39. The method of claim 38, wherein Z is O or methylene and  $R_2$  is OH.

5 40. The method of any of claims 13-24, wherein said compound is *N*-(2-hydroxy-3-(3-chloro-2-cyanophenoxy)propyl)-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine or a pharmaceutically acceptable salt or complex thereof.

41. A method of screening for a calcilytic compound  
10 comprising the step of measuring the ability of a compound to inhibit one or more calcium receptor activities, said compound having the formula:



wherein  $R_1$  is selected from the group consisting of:

15 aryl, longer-length alk, and cycloalk;

$R_2$  is selected from the group consisting of: lower alk, cycloalk, alkoxy, H, OH, =O, C(O)OH, C(O)O-lower alk, C(O)NH-lower alk, C(O)N(lower alk)<sub>2</sub>, SH, S-lower alk, NH<sub>2</sub>, NH-lower alk, and N(lower alk)<sub>2</sub>;

20  $R_3$  and  $R_4$  is each independently lower alk or together cyclopropyl;

$R_5$  is aryl;

$R_6$  if present is either hydrogen, lower alkyl or lower alkenyl; wherein  $R_6$  is not present if  $R_2$  is =O;

$Y_1$  is either covalent bond, alkylene, or alkenylene;

$Y_2$  is alkylene;

$Y_3$  is alkylene;

$Z$  is selected from the group consisting of: covalent  
5 bond, O, S, NH, N-lower alk, alkylene, alkenylene, and  
alkynylene, provided that if  $Z$  is either O, S, NH, or N-lower  
alk, then  $Y_1$  is not a covalent bond; further provided that  $Y_1$   
and  $Z$  may together be a covalent bond; and  
pharmaceutically acceptable salts and complexes thereof.

10 42. The method of claim 41, wherein said method is  
carried out under conditions wherein influx of extracellular  
 $Ca^{2+}$  is inhibited.

# INTERNATIONAL SEARCH REPORT

International Application No  
PC1/US 97/05558

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07C217/34 C07C217/14 C07C217/28 A61K31/135 A61K31/44  
A61K31/395 A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 40 40 186 A (HOECHST AG) 27 June 1991 see claim 1; example 8	1
X	EP 0 009 075 A (MERCK & CO INC) 2 April 1980 see abstract; claim 1	1,2
X	ES 480 066 A (ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES, S.A.) 1 April 1980 see page 2 - page 5	1
X	EP 0 002 792 A (SANDOZ AG) 11 July 1979 see claims 1,2	1
X	EP 0 188 361 A (GLAXO GROUP LTD) 23 July 1986 see claim 1	1
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

8 July 1997

Date of mailing of the international search report

17.07.97

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## INTERNATIONAL SEARCH REPORT

International Application No.

PC1/US 97/05558

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CH 636 856 A (SANDOZ AG) 30 June 1983 see page 5 - page 7 ---	1
X	DE 33 01 198 A (HOECHST AG) 19 July 1984 see page 14 - page 19; claim 1 ---	1,2
X	DE 29 43 406 A (BASF AG) 7 May 1981 see page 17 - page 18; claim 1 ---	1
X	DE 29 44 222 A (BASF AG) 14 May 1981 see page 13 - page 16; claim 1 ---	1,2
X	DE 25 02 993 A (HAESSLE AB) 4 September 1975 see claim 1; example 14 ---	1
A	WO 93 04373 A (NPS PHARMACEUTICALS INC) 4 March 1993 cited in the application see abstract ---	13
A	WO 94 18959 A (BRIGHAM & WOMENS HOSPITAL ;NPS PHARMA INC (US)) 1 September 1994 see abstract -----	13



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/05558

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 13-40  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.: 1, 2, 12, 41-42  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
see annex
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The vast number of theoretically conceivable compounds resulting from the combination of all claimed substituent definitions according to the formula of claim 1 precludes a comprehensive search.

The scope of the sought protection is also not well defined for the subject-matter of claim 1 due to vague expressions like "aryl", "longer-length alk.", "cycloalk.", "lower..", "alkylene"....

Claim 1 is also unclear in view of the definition of an aryl group (see also page 14 of the description) of the substituent R1 and the disclaimer (pyridyl = heteroaryl).

The definition given for R5 concerning substituted phenyl is also unclear because said substituted phenyl could have more than 5 substituents (4 + 3).

Guided by the description, the search has been limited to the domain of the examples which illustrates a common inventive concept. A comprehensive search cannot be carried out without going beyond what is technically and economically justified.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/05558

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/05558

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		EP 0637237 A	08-02-95
		JP 7506380 T	13-07-95
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# Foley & Lardner Time and Services Report

Printed on 05/18/2001 by Day, Joy A (JADAY)

Timekeeper: RSP      Richard M. San Pietro

Date: Thursday, May 17, 2001

Client: 026063	AMERSHAM PHARMACIA BIOTECH	Time: 4.00
Matter: 0101	LEE (USDC CASE NO. C-00-1937) (030516.0062)	
Phase:		
Task: 1	Normal time entry.	
Prac Grp: 208	Intellectual Property / Litigation	
Narrative: Edit and finalize papers for filing interference; meetings with R. Warburg to discuss strategy.		Open

Client: 026063	AMERSHAM PHARMACIA BIOTECH	Time: 1.90
Matter: 0102	MD (USDC #C98-01015 & C98-04167) (030516.0006)	
Phase:		
Task: 1	Normal time entry.	
Prac Grp: 208	Intellectual Property / Litigation	
Narrative: Review of Perkin-Elmer documents to determine earliest date Perkin-Elmer knew of Megabase.		Open

Client: 028614	DALHOUSIE UNIVERSITY	Time: 1.10
Matter: 0303	DALHO1130.US.2 -	
Phase:		
Task:		
Prac Grp: 208	Intellectual Property / Litigation	
Narrative: Final editing of declaration of Wright and Pohajdak.		Open

Client: 999800	ZZZ FOLEY & LARDNER-PROFESSIONAL DEVELOPMENT	Time: 2.50
Matter: 0301	INTELLECTUAL PROPERTY DEPARTMENT - GENERAL	
Phase:		
Task:		
Prac Grp:		
Narrative: Attend SDIPLA meeting.		Open

Totals for Thursday, May 17, 2001:

Billable Time (73.68%):	7.00
Non-Billable Time (26.32%):	2.50
<b>Total Time:</b>	<b>9.50</b>

Report Total:

Billable Time (73.68%):	7.00
Non-Billable Time (26.32%):	2.50
<b>Total Time:</b>	<b>9.50</b>